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Winsor, T.: Am. J. M. Sc. 230:133 (Aug.) 1955.
 Grimson, K. S.: J.A.M.A. 153:359 (June 4) 1955.
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 Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology 6:507 (Dec.) 1955.
 Strawn, J. R., and Moyer, J. H.: Personal communication, 1955.
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- 2. Pence, L. M.: Texas State J. Med. 50:290 (May) 1954.
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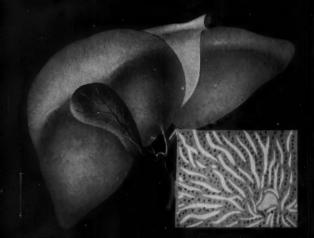
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*Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Washington, D. C., National Academy of Sciences—National Research Council, 1952, p. 21.



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References: 1. Boland, E. W., J.A.M.A. 160:613 (February 25) 1956. 2. Margolis, H. M. et al., J.A.M.A. 158:454 (June 11) 1955. 3. Bollet, A. J. et al., J.A.M.A. 158:459 (June 11) 1955. 'CO-DELTRA' and 'CO-HYDELTRA' are trademarks of MERCK & Co., INC.



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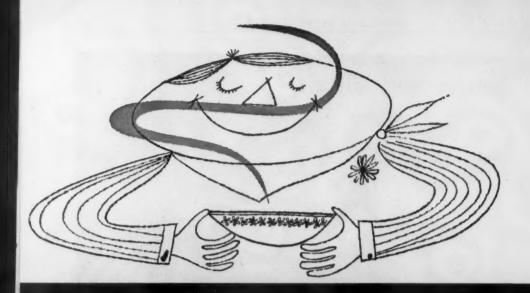
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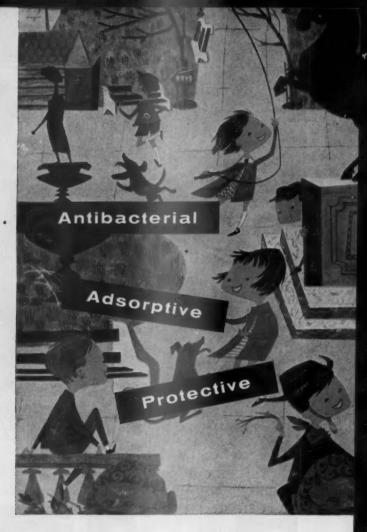




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1. Russ, J.D.: Personal communication.

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Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105

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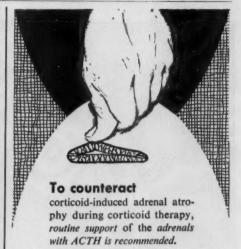
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- Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1955, p. 754.

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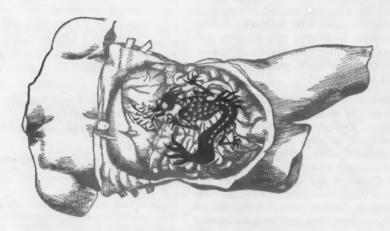
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- Haverback, B.J.; Stevenson, T.D.; Sjoerdsma, A., and Terry, L.: The Effects of Reserpine and Chlorpromazine on Gastric Secretion, Am. J. M. Sc. 230:601 (Dec.) 1955.

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Lemere, F.: Northwest Med. 54: 1098, 1955.

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Sokoloff, O. J.: A.M.A. Arch. Dermat. In press.

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Thimann, J. and Gauthier, J. W.: Quart. J. Stud. Alcohol. 17: 19, 1956.

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1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation, Journal-Lancet, 73:414 (Oct.) 1953.

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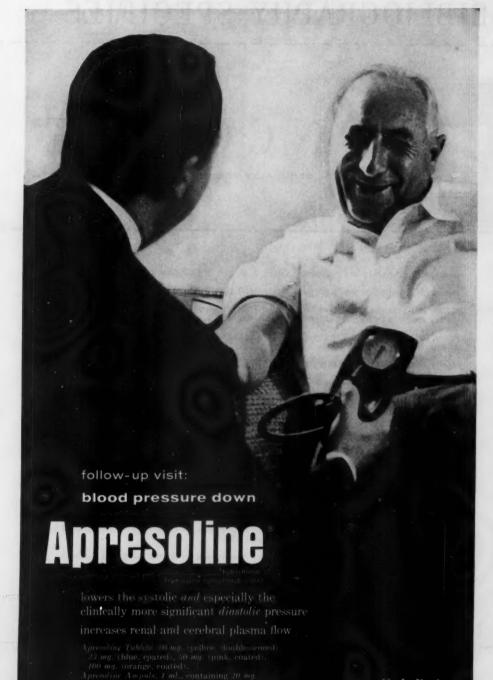
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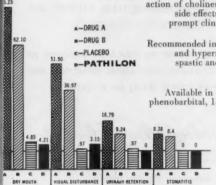
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1. Council on Pharmacy and Chemistry, J.A.M.A. 160:889 (Feb. 4) 1956.
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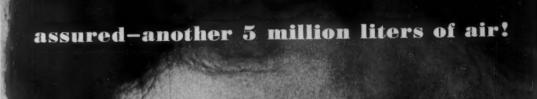
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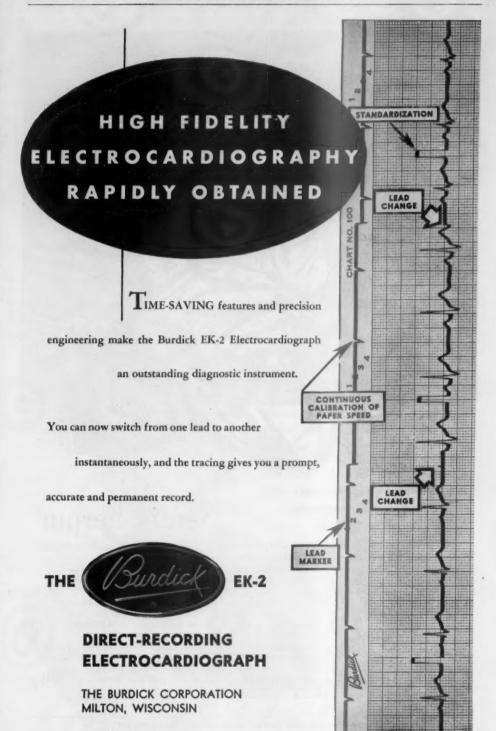
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1. Chambartan, D. 7.; Sastroenf. 17:224-5, 1911 D. C.; South, M. J. 45:1139, 1952, 3. Pakulis, 3.

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Adults—2 capsules or 2 teaspoonfuls of syrup, t.i.d. before or after meals. If necessary repeat at bedtime.

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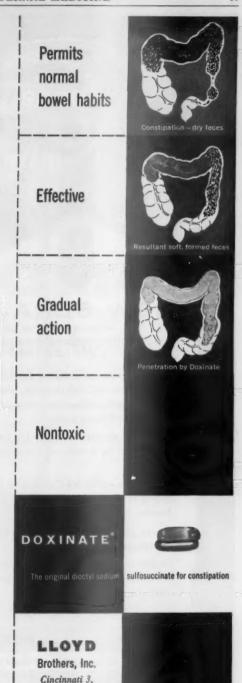
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Adults: one green 60 mg. capsule daily or one to three orange 20 mg. capsules daily.

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REFERENCES:

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 Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1; 28-39 (Jan.) 1950
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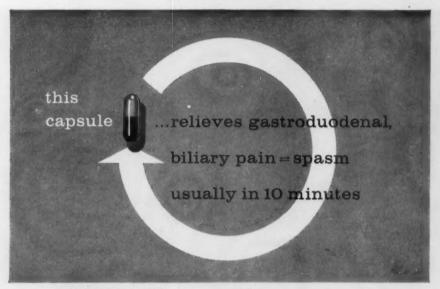
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1. Moser, M. New York State J. Med. 55 1999 (July 15) 1955. 2. Agrest, A., and Hoobler, S.W.: J.A.M.A. 157:999 (March 19) 1955. 3. Smirk, F.H.: Am. J.



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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.





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 Balfour, D. C., Jr.: Am. J. Gastroenterol. 22:181, 1954.
 Burke, J. O., et al.: Internat. Rec. Med. & Gen. Practice Clin. 167:587, 1954.
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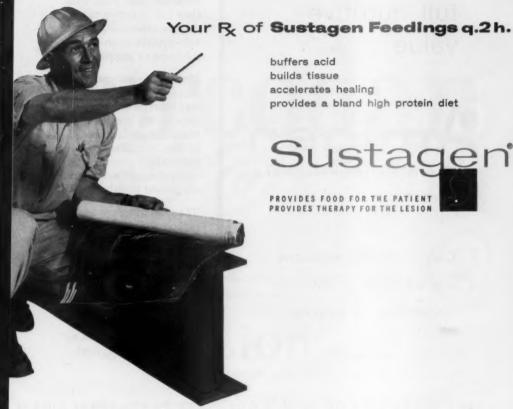
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THE PRESENT STATUS OF ETIOLOGIC DISCOVERY IN VIRAL DISEASES *

By JOHN F. ENDERS, Ph.D.,† Boston, Massachusetts

It is a distinguished honor to be invited to address this College, and in particular to be asked to deliver the Bruce Memorial Lecture in Preventive Medicine. I would take this opportunity to express in the presence of so many of America's physicians my gratitude for the collaboration that certain members of your profession have throughout the years given to me as an investigator. Without it, our work would have been impossible. Upon this sort of happy relationship between doctors, public health officers, and those in the laboratory, the progress of modern preventive medicine has in large measure depended.

I have chosen in this lecture to comment on the present status of etiologic discovery in viral diseases. To treat this topic within the span of half an hour in any complete or systematic manner is obviously impossible. I shall, accordingly, indicate briefly the advances that have been made during the last 25 years in the definition of viruses causing or associated with illness in man. Then I shall refer to certain factors which appear to have contributed to these advances. Finally, by way of illustrating and emphasizing the fact that the era of etiologic discovery is not finished, but rather is at the beginning of another interesting and exciting phase, I shall consider in more detail certain viruses or groups of viruses that have very recently been The relationship of a number of these agents to disease has not yet been conclusively established. This uncertainty, however, renders even more intriguing the demonstration of their presence within the human body.

* Presented as the Bruce Memorial Lecture at the Thirty-seventh Annual Session of

The American College of Physicians, Los Angeles, California, April 17, 1956.

† Chief, Research Division of Infectious Diseases, Children's Medical Center, Boston, and Professor of Bacteriology and Immunology at the Children's Hospital, Harvard Uni-

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THE LAST TWENTY-FIVE YEARS—A CONTINUING PERIOD OF ETIOLOGIC DISCOVERY

During the last 25 years a surprisingly large number of new viral agents responsible for illness in man has been revealed. It is interesting and instructive to recall that many virologists working in the 1920's did not foresee the rich harvest that was to follow. At that time, as I remember, the feeling was prevalent that the age of etiologic discovery had almost, if not completely, come to an end. In a few diseases, such as influenza, it was generally admitted that the agents would in due time be demonstrated. But once this "mopping up" was accomplished, the search for others would not be profitable.

Certain Viral, Diseases of Man*
(Arranged according to period evidence for viral etiology was first obtained)

Before 1910	1910-1919	1920- 1929	1930-1939	1940-1949	1950-1955
Rabies Poliomyelitis Smallpox-vaccinia- cowpox infections Yellow fever Dengue Phlebotomus fever	Measles Varicella Herpes zoster Herpes simplex Inclusion conjunc- tivitis Verrucae		Encephalitides St. Louis Japanese B Equines Russian far east Influenza Psittacosis-lympho- granuloma infec- tions Mumps Rubella Lymphocytic choriomeningitis Rift valley fever	Infectious hepatitis Serum hepatitis Colorado tick fever Epidemic viral gastroenteritis	Coxsackie infection: (Pleurodynia Herpangina Meningitis Myocarditis) APC-RI-ARD infections (undifferen tiated acute respiratory disease pharyngeal-con- junctival fever) ECHO infections (meningitis) Boston exanthem

* In compiling this table certain human infections of rare occurrence caused by viruses primarily attacking lower animals have been omitted (e.g., the viruses of foot-and-mouth disease, ovine pustular dermatitis, Newcastle disease, etc.). Others also not included are certain exotic infections (e.g., when Nile, Bwamba fever, etc.). The evidence available at the dates indicated in the table for accepting a virus as causative agent varied. In the majority of cases it consisted in the reproduction of diseases either in man or experimental animals with materials considered to be free of bacteria or other microörganisms. Usually such evidence was reinforced either at the time or subsequently by demonstration of the agent's filterability and the development of specific antibodies during the course of the infection. In other instances, where no susceptible animal was known and experiments in man were not carried out, the essential evidence consisted in the constant association of the agent with the disease and the demonstration of the development of specific antibodies during its course. While it is realized that data of this sort alone have not inevitably served to establish the etiologic factor as a virus, they have proved sufficiently accurate, in our opinion, to be accepted as a basis for the rough chronologic analysis attempted here.

How inaccurate was this view is stressed by simply tabulating certain of the more common or important viral diseases of man in relation to the time when the first acceptable evidence regarding the nature of the etiologic agent was obtained. In table 1, I have made this correlation. It is apparent that by the year 1910 there were grounds for concluding that four most notable diseases—smallpox, yellow fever, rabies and poliomyelitis—were viral infections, as were dengue and sandfly fever. During the next 10 years several other entities were included in this class. They were, however, on the whole of less significance from the clinical standpoint.

The stream of discovery at the beginning of the following decade suddenly seemed to cease. No significant contribution was made until near the close of this period when, in 1928, the classic experiments of Stokes, Bauer and Hudson 1 provided new and indisputable evidence that yellow fever was caused by a virus. This conclusion, it will be remembered, had been rendered doubtful by Noguchi's claim in behalf of a spirochetal origin for this disease.

Shortly after the settlement of this controversy, the waters of the stream -to continue the metaphor-again began to flow in unexpected volume. In the 1930's nearly as many viral infections were established as during the preceding period of over 30 years. Although, numerically, determinations of this kind declined during the 1940's, the demonstration that infectious and serum hepatitis were caused by an agent or agents behaving like viruses was of the greatest moment. It was also at the end of this period, in 1948 to be exact, that the Coxsackie group—the first of three large groups of viruses-was revealed by the researches of Dalldorf and Sickles.2 Unlike the majority of viruses, these agents were first isolated from the feces. Accordingly, the question of their pathogenicity for man remained temporarily in doubt, and it was only later that data indicating their relationship to the conditions that I have listed in the last column of the table were forthcoming. Similarly, doubt existed—and, indeed, still exists—in respect to the etiologic status of the so-called "ECHO" group, as well as of certain members of the APC-RI-ARD, or respiratory-tract disease family,* which have been identified during the last five years.

Because of the revelation of these groups of viruses and the isolation of others which are as yet incompletely described, we can distinguish in the present time another period of accelerated etiologic discovery.

FACTORS RESPONSIBLE FOR THE CONTINUING ADVANCE IN THE ETIOLOGY OF VIRAL INFECTIONS

Before discussing certain of these more recent findings, I shall, as additional background, mention two factors which seem to me to have been

largely responsible for this continuing advance.

First is the fact that the existence of a number of diseases exhibiting the characteristics of an infectious process has been recognized only within comparatively recent years, whereas others, known for a longer time but of rare occurrence or poorly defined from the clinical standpoint, suddenly increased in incidence and so became objects of more general interest and concern. As examples may be mentioned St. Louis encephalitis, which was first observed in 1932, as well as western and eastern equine encephalitis, which as illnesses of man were first described in 1932 and 1938, respectively. Psittacosis and serum hepatitis afford illustrations of rare or obscure infections to which little attention was paid during the early years of the century, but which later were studied intensively because of an abrupt increase in prevalence. Thus the occasion—to borrow the Hippocratean

^{*}While this manuscript was in press a note appeared by a group of interested investigators recommending that the term "Adenoviruses" be adopted for these agents. See Science 124: 119, 1956.

phrasing—has continued to be instant and therefore stimulating to etiologic researches.

The second factor relates to methodology. It is remarkable that nearly all the biologic technics applied today to the study of the animal viruses were in use soon after foot-and-mouth disease virus, the first representative, was discovered in 1898. Thus, by 1914, each of the known means of cultivation had been employed, i.e., the living mature animal, the avian embryo, and the tissue culture. Also at an early date, certain procedures of the immunologist were added to the virologist's technical repertoire. It is remarkable that, with the exception of the technic of viral hemagglutination. described by Hirst in 1941, and those taken directly from chemistry and physics, no essentially new procedures have since been devised. Technical advances, therefore, have consisted chiefly in modification or refinement of the original methods. These changes have nevertheless proved to be of much importance in promoting progress. Yet even more important has been the realization from time to time on the part of virologists that the potentialities of the older methods had not been completely exploited. I shall support these last statements by two illustrations, one taken from the older and one from the more recent literature.

Although the monkey had been used successfully by Landsteiner and Popper in 1909 for the isolation of poliomyelitis virus, this animal, for reasons that are not entirely clear, was little employed in the study of other diseases suspected to be caused by viruses until in 1928 the dramatic experiments on yellow fever by Stokes and his associates, to which I have already referred, reëmphasized its usefulness. Isolation of the yellow fever virus in monkeys enabled Theiler to show that it could also be adapted to the white mouse. This demonstration, in turn, contributed much to the general recognition of the value of the mouse as an experimental animal. It is therefore perhaps not surprising that nearly all of the new viruses described during the fruitful period 1930 to 1940 were first isolated in either the monkey or the mouse.

My second illustration of how the old methods have been made more productive is drawn from recent work with tissue culture technics as applied to various problems in virology. Ever since 1914, a variety of species have from time to time been cultivated in vitro. No manifestations, however, were consistently observed within the culture itself whereby the multiplication of the agent could be recognized. To demonstrate multiplication, it was necessary to inoculate material from the culture into a susceptible animal. For most purposes, therefore, the tissue culture offered no advantage over the living animal. This defect of the culture was, however, eventually overcome. Huang 4 in 1942 noted that, following the growth of equine encephalitis virus in cultures of chick embryonic tissue, cell degeneration regularly ensued. Here, obviously, was a criterion of multiplication within the system itself that was as easily discernible as death or

pathologic changes in the tissues of the infected animal. Little or no attention, however, was paid to Huang's significant observation, possibly because it was made during the war years.

In 1949 Dr. Robbins, Dr. Weller and I 5 succeeded in propagating polioviruses in cultures of a variety of extraneural human tissues. Soon thereafter we noticed that degenerative changes regularly occurred in various types of cells infected with the virus.6 We realized that this phenomenon provided a means more rapid and convenient than the experimental animal of determining the presence of these agents, and we indicated how cell degeneration caused by the virus might be used to measure the infectivity of suspensions of the viruses and to identify their specific antibodies. Since these observations were made, it has been found by other workers as well as ourselves that many viral species, when grown in cultures of susceptible cells. consistently exhibit "cytopathogenicity," i.e., the capacity to injure or destroy the cells in which they multiply. Because of these findings, and because of recent improvements in the technic of tissue culture, such as the use of antibiotics and those introduced by Dulbecco,7 the method as now used in virologic work may be compared in usefulness to the broth tube or the agar plate for the isolation and study of bacteria. How valuable the method has become is well demonstrated by the fact that all the newly recognized viruses—with the exception of the Coxsackie group, that I shall now rapidly discuss-were first isolated in tissue culture.

REMARKS ON CERTAIN VIRUSES RECENTLY IDENTIFIED

The agents I have selected for particular comment are, with one exception, all members of the three large groups or families that have been recently identified, i.e., the Coxsackie, the ECHO and the respiratory-tract disease group. The exception is a virus that was isolated in 1955 by McCarthy, Cheatham and Mitus in my laboratory from fatal cases of giant cell pneumonia, and that I include for the purpose of emphasizing the fact that in these days other new viruses are being encountered with surprising frequency.

The Coxsackie Viruses: The first representatives of the Coxsackie family were demonstrated by inoculating into suckling mice fecal suspensions from patients with symptoms of poliomyelitis. Largely through the use of these animals, which had been little employed by previous investigators, the following facts concerning the Coxsackie viruses have been established:

- They are small, being approximately the size of poliovirus, i.e., about 30 mμ in diameter.
- They are frequently encountered in the human gastrointestinal tract in health and disease.
- They are divisible into two large groups, designated A and B, on the basis of differences in the pathologic changes they produce in suckling mice.

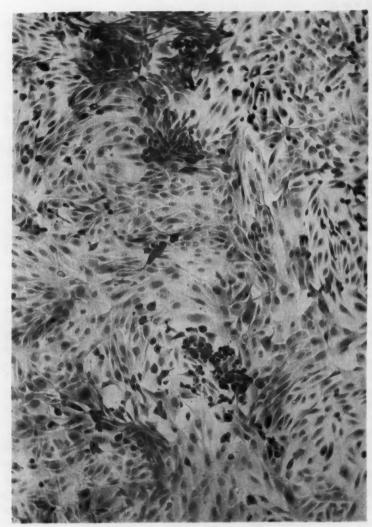
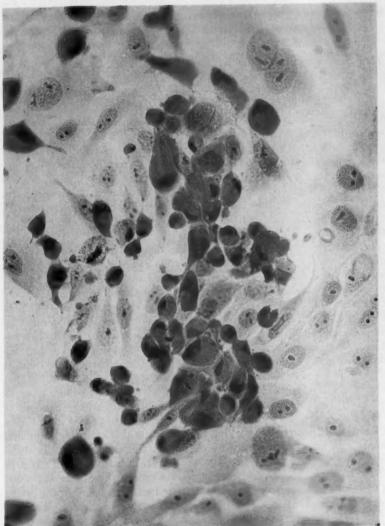


Fig. 1. Effect of Coxsackie virus B₂ (Ohio) in a culture of trypsinized monkey kidney cells. Focal areas of cells showing cytopathic changes (24 hours after inoculation of virus). (H. & E.) × 105.



A focus of injured cells from same culture as shown in Fig. 1. Note crescentic pyknotic nuclei and intense eosinophilic staining of cytoplasm (24 hours after inoculation of virus). (H. & E.) ×430. 3 Fig. 2

- They are antigenically heterogeneous: at least 19 antigenic types have been distinguished among Group A strains and five among Group B strains.
- 5. In cultures of human or monkey cells only four Group A types are cytopathogenic, whereas all Group B types cause cell degeneration (figures 1 and 2).

Their pathogenic properties for man have been and probably will continue for sometime to be the subject of active investigation. As yet it has not been determined whether any of them can initiate paralytic disease, although Group A strains have often been isolated from the feces of patients with paralytic poliomyelitis. In nearly all such instances, however, poliovirus has also been recovered. On the other hand, there is more suggestive evidence for their participation in aseptic meningitis, which, of course, cannot be distinguished on clinical grounds from nonparalytic poliomyelitis. Several workers have isolated Coxsackie viruses, identified as members of the B group, from spinal fluid. The Moreover, the development of antibodies specific for the type of virus isolated has been demonstrated in many cases of aseptic meningitis as well as in all the other conditions where Coxsackie viruses are presumably implicated.

The data are now sufficient to indicate that epidemic pleurodynia, or Bornholm disease, is a Coxsackie virus infection and is usually, if not always, caused by Type B strains. Pleurodynia was perhaps the first clearly defined nosologic entity in which satisfactory evidence for Coxsackie virus as causative agent was obtained. Thus, Curnen, Shaw and Melnick ¹¹ in 1949 first isolated one of these viruses from a patient with typical symptoms. In 1950 Weller, Enders, Buckingham and Finn, ¹² stimulated by this observation, recovered several strains of Group B virus from stored feces and throat washings collected during an extensive outbreak that occurred in Boston in 1947, ¹⁸ and demonstrated increases in homologous antibody during the course of the disease in a number of patients. Similar findings have in general been reported by various authors in this country and in Europe. ⁸

The most recent correlation between Coxsackie viruses and human disease has been made in cases of a highly fatal myocarditis occurring in infants which is sometimes accompanied by meningitis and encephalitis. In 1952 Gear and his co-workers ¹⁴ in South Africa investigated 10 such cases in newborn children. Death occurred in six. Three of these were examined post mortem and acute severe myocarditis was found in each. In the brains of two of the fatal cases, suggestive evidence for the presence of Coxsackie B virus was obtained. An additional small outbreak has been studied by these workers, ¹⁵ who subsequently succeeded in isolating a B Type 3 virus from the myocardium of another fatal case. In 1953 Dr. Sidney Kibrick, ¹⁰ my associate, recovered in tissue culture the same virus type from the spinal cord of an infant who died five days after delivery by section. Postmortem examination revealed focal myocarditis as well as focal encephalitis and

meningitis. It is of much interest that the mother underwent a minor illness a few days before the child was delivered. This event, as well as the time relationships, suggests that infection of the infant occurred in utero.

Coxsackie A viruses, in contrast to the B group, appear on the whole to be less virulent for man. The etiologic role of Coxsackie A viruses in herpangina has, indeed, been unequivocally demonstrated by Huebner and his associates. But this is a relatively mild disease. Group A viruses have also been occasionally associated with several minor illnesses, variously described as grippe, influenza or summer diarrhea. Their connection with aseptic meningitis, although probable, has not been definitely established.

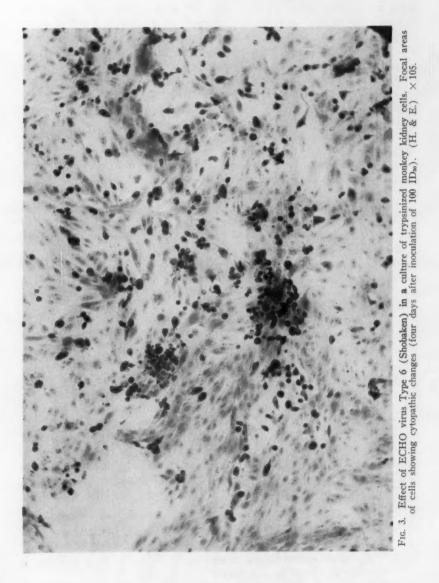
For me, two old lessons have been retaught by this modern history of the Coxsackie viruses which I have sketched so imperfectly. The first points out how even minor modifications in technic may lead to results of great significance; the second, how difficult it is to establish beyond cavil

an etiologic relationship.

ECHO Viruses: The discovery of the Coxsackie family was followed within two years by the recognition of the primary representatives of another sizable group of viruses with certain common properties and inhabiting the enteric tract of man. In the course of their first investigations on the direct isolation of poliomyelitis viruses from human feces by the tissue culture method, Robbins, Enders, Weller and Florentino 17 in 1950 encountered cytopathogenic agents that could not be classified among any of the known viruses. Since that time large numbers of these new viruses have been recovered in different laboratories, 18 and a beginning has been made toward their more precise characterization and pathogenic significance. Because they could not immediately be implicated as agents of human disease, they were designated by various names, such as "orphan viruses," "atypical viruses" and "human enteric viruses." In an attempt to resolve the confusion that arose because of this diversity in nomenclature, an unofficial committee of interested virologists 18 recently proposed that these viruses should be provisionally classified as the "enteric cytopathogenic human orphan," or ECHO group. Realizing that the group was heterogeneous and might well include several different species, the committee recommended that if and when any antigenic type is identified as the etiologic agent of a clinically distinct disease it should be removed from the ECHO group.

The general characteristics of the ECHO viruses as so far defined are as follows:

- 1. They are antigenically heterogeneous. Already 14 antigenic types have been delineated, and it is almost certain that others will be added.
- They do not cause disease in suckling mice, nor is there evidence as yet that any other animal species is susceptible.
- They are not related to other viruses found in the human alimentary tract.





A focus of injured cells from same culture as shown in Fig. 3. Note similarity of changes to those produced by Coxsackie virus (Cf. Fig. 2.) (H. & E.) ×430 F1G. 4.

4. They are cytopathogenic for the cells of certain primates, including man. The cytopathogenic effects of some, but not all, ECHO types can be distinguished from those of polioviruses. They resemble in certain instances the effects of the cytopathogenic Coxsackie viruses (figures 3 and 4).

Their relationship to clinically apparent disease in man has not yet been conclusively established. That they frequently give rise to inapparent infection, however, is certain, since several workers, 19, 20 including ourselves, have demonstrated in numerous instances the development of antibodies specific for the strain of ECHO virus recovered from the same individual. Furthermore, human gamma globulin has been shown to contain neutralizing

antibodies against several different types.

The problem of ECHO viruses as incitants of overt disease appears so far to center about the question of whether they can cause illness resembling nonparalytic and mildly paralytic poliomyelitis, since nearly all strains recovered from sick persons have been derived from patients exhibiting symptoms compatible with these conditions. In many of these patients, no other viral agent has been shown to be present. Moreover, in certain of these individuals no antibodies against any of the polioviruses have been detected. As an example of the findings obtained by several workers, I shall summarize our own data recorded during tests carried out as a part of the Polio Vaccine Field Trial in 1954. Laboratory studies on 46 cases of mildly paralytic and nonparalytic illnesses in vaccinated children and controls resulted in the recovery of 32 agents from each of 32 individuals. Three of these agents were identified as polioviruses and three as members of the Coxsackie group. Twenty-five have been classified as ECHO Type 6. The sera of approximately one-half of the children from whom an ECHO virus was isolated have been tested. In each a significant increase in antibody reacting with the agent was recorded. In only two cases among those shedding ECHO viruses in the feces was an increase in antibodies against the polioviruses observed.

As I have indicated, experiences comparable to ours have been reported from other laboratories. There is, accordingly, much reason to believe that certain types of ECHO viruses may be responsible for a proportion of cases diagnosed clinically as nonparalytic poliomyelitis. Moreover, the possibility exists that, on occasion, they may also induce a mildly paralytic disease. More information is of course required before ultimate decisions concerning these questions can be reached, since ECHO viruses have been obtained by Sabin,²¹ Hammon ¹⁸ and others from large numbers of normal

children in various parts of the world.

Respiratory Tract Disease Viruses: The members of this new and widespread group have been variously termed adenoidal-pharyngeal-conjunctival, RI (respiratory infection) and acute respiratory disease viruses by their discoverers or by those who have related them to definite disease entities.²²⁻²⁴ This varied nomenclature makes reference to these agents difficult and somewhat awkward. It is hoped that a uniform terminology will be adopted in the future. Like the Coxsackie and ECHO families, they are distinguished by antigenic heterogeneity. Thirteen or 14 antigenic types have been established, and more bid fair to come. (At this point, I'm sure you are tempted, as I am, to cry out in anguish, like Macbeth upon seeing the vision of Banquo's endless descendents, "Will the line stretch out to the crack of doom?") Like the ECHO group, APC viruses have failed to produce disease in mice but are all cytopathogenic in cultures of primate cells. Indeed, the first isolations, by Rowe and Huebner,22 were made unexpectedly in uninoculated cultures of adenoidal tissue removed from apparently normal children. The virus latent in these tissues multiplied after a time, causing cell degeneration. HeLa carcinoma cells have proved particularly sensitive to the injurious effect of these viruses. Peculiar alterations in the nucleus of infected cells are characteristic, and serve as a differential criterion between these agents and others that may be found in the alimentary tract (figures 5 and 6).

As Rowe and Huebner have shown, a number of types have not been associated with illness but appear to remain latent in the tonsils and adenoids. There are now, however, good grounds for accepting Types 3, 4 and 7 as etiologic agents in the grippelike illness occurring in recruits and designated during the last war as "undifferentiated acute respiratory disease" by the Army Commission on Respiratory Diseases. This evidence consists of (1) frequent association of these viruses with recent epidemics in military personnel, 24, 26 (2) antibody increase in patients' sera, 22, 24, 26 and (3) the retrospective demonstration of increases in specific antibodies in the serum of volunteers inoculated experimentally with throat washings taken

from patients during the war.24

There can also be little or no doubt that Type 3 strains may cause non-bacterial pharyngitis. Huebner and his associates studied one form of this condition which occurs in children during the summer season, and which they termed "pharyngoconjunctival fever." Besides recovering the virus from a high proportion of cases and demonstrating increases in specific antibodies, they reproduced the disease in volunteers by inoculating the conjunctiva with tissue culture-grown virus.

In addition to these conditions, in which the etiology has apparently been established, it is probable, on the basis of the findings of Hilleman and his associates,²⁸ that primary atypical pneumonia unassociated with cold ag-

glutinins is a result of the activity of the same agents.

Among the many unsolved problems presented by the discovery of these viruses, two seem of particular interest. First, we may speculate briefly concerning the significance of the apparent ubiquity in tonsillar and adenoidal tissues of several antigenic types that have not yet been related to overt disease, and ask what may be the effect of this silent infection if it

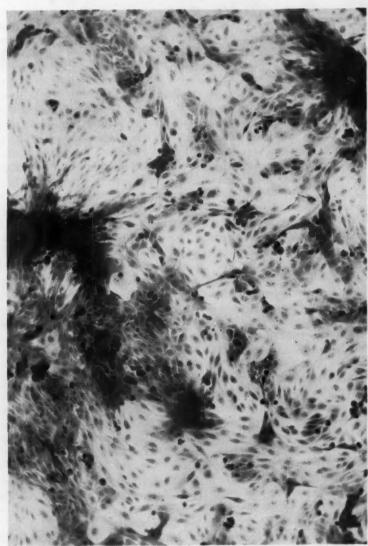
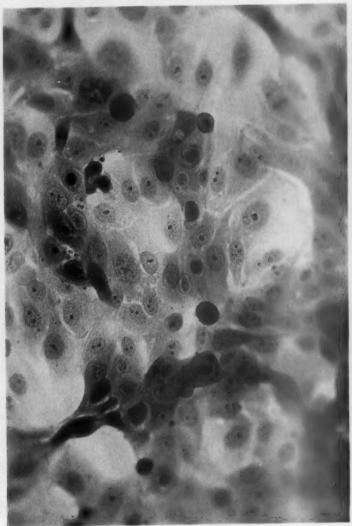


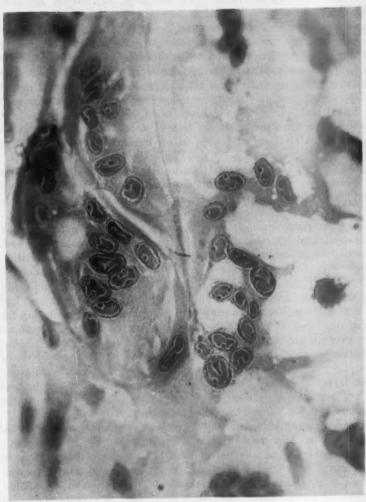
Fig. 5. Effect of APC virus-type unknown—in a culture of trypsinized monkey cells. First passage (four days after inoculation). Note focal areas of injured cells, some of which exhibit densely staining nuclei.



A focal area in same culture as shown in Fig. 5. Central condensation of nuclear material into masses reminiscent of inclusion bodies is characteristic. F1G. 6.



Fig. 7. Effect of virus recovered from a case of giant cell pneumonia in a culture of trypsinized human kidney cells (16 days after inoculation of virus). Note syncytia with aggregation of nuclei. (H. & E.) ×105.



An affected area from same culture as shown in Fig. 7. Eosinophilic intranuclear inclusions are prominent. (H. & E.) ×430. 00 Fig.

proves to be of marked chronicity. Can it, under appropriate stimulation, like herpes simplex, burst forth into manifest disease? If so, what would be the characteristics of this disease? Would they, for instance, appear to resemble those of the common cold?

The second problem I would mention lies in the possibility that certain of these viruses may cause disease of other organs. Kjellen ²⁷ in Sweden has already found APC virus associated with mesenteric adenitis, and these agents have frequently been recovered from feces. ²⁰ Indeed, it was from such material, obtained from a patient with roseola infantum, that a very early representative of this family was described by Neva and Enders ²⁸ before the existence of the group was recognized. We might inquire, therefore, whether the virus present in the feces is merely a passenger from the upper alimentary tract, or originates in an infection of the intestine or adjacent structures.

Giant Cell Pneumonia Virus: * In conclusion, I shall rapidly describe the salient features of two viruses exhibiting identical properties that my associates, Dr. Kevin McCarthy, Dr. William Cheatham and Dr. Anna Mitus, in 1955 recovered in tissue culture from two fatal cases of giant cell pneumonia.20 This rather rare disease often represents the terminal event in children debilitated by other illness. Although a rash is not associated, the possibility that measles virus might be involved has been advanced on pathologic grounds.³⁰ Opportunity to test this hypothesis was afforded, since Dr. Peebles and I had succeeded two years ago in isolating and maintaining the virus of measles 31 in cultures of human kidney cells, and had shown that both specific neutralizing and complement-fixing antibodies for the virus developed in patients during convalescence. In tissue cultures the measles virus produces a characteristic effect. Certain cells at different sites in the even sheet of normal growth coalesce to form large syncytia or multinuclear giant cells. Within the nuclei of the giant cells, eosinophilic inclusion bodies develop. This peculiar cytopathogenic effect can be prevented or "neutralized" if the virus is mixed with serum containing the homologous antibody before addition to the culture.

The two viruses, derived from the tracheal secretion and lung tissue, respectively, of the subjects with giant cell pneumonia, produced cytopathic changes in renal epithelial cells indistinguishable from those characteristic of measles virus. Convalescent phase measles serum mixed with giant cell pneumonia virus prevented their development (figures 7 and 8). Additional evidence for the close relationship or identity of measles and giant cell pneumonia virus was obtained in cross neutralization and complement-fixation tests employing convalescent phase serum of monkeys that had

been infected with one or the other agent.

If it is finally established that the giant cell pneumonia virus is identical

^{*}The studies on the giant cell pneumonia and measles viruses were conducted under the sponsorship of The Commission on Viral Infections of the Armed Forces Epidemiological Board and supported by the Office of the Surgeon General, Department of the Army.

with that of measles, then the interesting fact will emerge that measles virus, under certain conditions, can give rise to a disease that, from the clinical

standpoint, is quite unrecognizable as rubeola.

I have now finished this attempt to suggest the present active state of etiologic discovery in the field of viruses and to distinguish certain elements that set it in motion. I have a sense of having been overambitious, since it has continuously been necessary to refer hastily and incompletely to complex and still unresolved problems. I shall be satisfied, however, if I have managed to convey to you a little of the excitement and pleasurable anticipation we who are engaged in the study of these phenomena are now experiencing.

SUMMARIO IN INTERLINGUA

Es interprendite le essayo de summarisar le plus importante discopertas recente de viruses como agentes de morbo human. Introductorimente, un breve revista es presentate del resultatos de studios etiologic durante le passate 25 annos, insimul con un analyse de certes del factores que es considerate como responsabile in parte pro le non-expectate progressos facite durante iste periodo. Postea, es delineate le stato presente del exploration de relationes etiologic inter certe novemente recognoscite viruses e morbos in humanos. Iste delineation include discussiones del rolo del gruppo Coxsackie, del gruppo ECHO (= Enteric Cytopathogenic Human Orphano), e del recentemente definite gruppo respiratori APC-RI-ARD. In conclusion, es describite le effectos cytopathogenic de un virus isolate per le associatos del autor ab casos de pneumonia a cellulas gigante. Iste virus es similissime o identic al agente etiologic de morbillos. Datos justificatori del association de illo con iste relativemente rar forma de pneumonia es mentionate brevemente.

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THE IMPORTANCE OF THE FRACTIONAL SERUM BILIRUBIN DETERMINATION IN CLINICAL MEDICINE*

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It was the great contribution of Hijmans van den Bergh and his associates, Snapper and Muller, to apply the Ehrlich-Proscher diazo reaction for bilirubin to the bilirubin of blood serum and body fluids in qualitative and quantitative fashion.1,2 This work, which appeared during and just at the end of World War I, gave a new impetus to the study of jaundice, liver disease and the anemias. In the subsequent years an extensive literature has accumulated on the subject, from both fundamental and clinical points of view. There is universal agreement on the specificity and general value of the total serum bilirubin determination. In view of the ease and simplicity of the method now available, it is surprising that it has not fully replaced the icterus index determination, which is much less specific and at times grossly misleading, substances such as hemoglobin, carotene and hematin in particular giving rise to false elevation, often of considerable degree. Van den Bergh recognized that the precipitation of the serum proteins with alcohol or acetone, as in his quantitative technic for the indirect and total bilirubin, resulted in loss of a certain fraction by adsorption on the precipitated pro-The colorimeters then in use were relatively insensitive and did not permit a primary dilution of the serum, but with the advent of the photoelectric colorimeter Malloy and Evelyn 3 showed that, by a preliminary fivefold dilution of the serum with water, the addition of alcohol and the subsequent indirect diazo reaction proceeded just as well without protein precipitation, and the increased sensitivity of the colorimeter permitted quantitative determination despite the relatively great dilution.

The fractional serum bilirubin determination has been less widely accepted, for reasons that will now be considered. One of the main objectives of the present communication is to emphasize the increased value, from a clinical standpoint, of the fractional determination as used for many years in this laboratory.^{4, 5}

It will be remembered that van den Bergh carefully described two main types of diazo reaction: a direct and an indirect, the first without the use and the latter with the use of alcohol. There is a wide diversity of opinion as to

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the basic significance and clinical importance of these types. An extensive literature has accumulated on this subject, of which, at the present time, only a few of the more pertinent contributions will be considered. There has been a good deal of confusion about terminology, due at least in part to insufficient attention to what van den Bergh actually said. We have cited certain of his statements in an earlier publication,5 but it is perhaps of sufficient importance to repeat these, in part, in the following. Van den Bergh used the term "direct" in the sense of a rapidly occurring reaction ("schnell eintretende") or what Feigl and Ouerner 6 subsequently designated as "prompt direct" reaction. Van den Bergh 2 clearly included the delayed direct reaction with the indirect. Thus he states: "The direct reaction occurs in all cases in a few seconds, at the most 30 seconds": while of the indirect he says: "Of these it is true that a reaction also occurred without addition of alcohol, but this commenced considerably later-there was an interval of 2, 3, 4 minutes or longer before the reaction began to become definite and still longer until it reached its greatest intensity. If one repeated this experiment with addition of alcohol then the reaction occurred maximally almost in the same moment." Thus it was logical for Feigl and Querner 6 to distinguish sharply between "prompt" and "delayed" direct types, and to suggest the term "biphasic" for serum samples exhibiting both components. The latter term, however, is believed superfluous, as all icteric sera exhibit diazo reactions that are biphasic in some degree. It is interesting that Feigl and Ouerner, whose early work deserves much more attention than it has received, emphasized the importance of the delayed type in the following terms: "The delayed reaction relates to a definite modification of bilirubin and is typical for toxemic and hemolytic conditions." From the clinical point of view, the latter is in essential agreement with our own experience if one substitutes parenchymal or hepatocellular for toxemic, as will be discussed later.

Other differences between the direct and the delayed or indirect types were soon recorded. The latter is chloroform-soluble ^{7,8} or nonpolar, the direct type water-soluble or polar. The polar and nonpolar behavior of the two types has been particularly emphasized in the recent studies of Cole and Lathe, ^{9, 10, 11} as will be discussed more fully later. The direct type is much more readily oxidized to biliverdin, whereas the indirect is relatively stable. Significant differences in spectral distribution curves were observed by Sheard and Davis. ¹² Despite these differences and the early confirmation of the correctness and significance of van den Bergh's observations, there has been considerable tendency, especially in more recent years, to minimize the importance of a fractional bilirubin determination, and to emphasize only the total serum bilirubin. ¹⁸⁻¹⁷

Although van den Bergh clearly recognized the delayed direct reaction and separated it from the immediate or prompt direct, he did not attempt to determine these fractions quantitatively, most likely because of the relative

inaccuracy and insensitivity of the colorimeters then available. Malloy and Evelyn measured the direct reacting bilirubin at 30 minutes after addition of the diazo reagent and total bilirubin after addition of alcohol to the 5x diluted serum. It is apparent from van den Bergh's statement, given in the foregoing, that measurement of the direct bilirubin at 30' would include a considerable proportion of the delayed reacting component—in other words, of bilirubin having the same significance as the indirect reacting type. This is fully confirmed in the present study, as will be shown in the following. On the basis of van den Bergh's emphasis that a very short interval encompasses the prompt direct reaction, Ducci and I suggested in 1945 that the direct measurement be made at one minute and the total after the addition of alcohol as according to Malloy and Evelyn.8 A further study of this fractionation was reported by Ducci and Roeschmann in 1949,18 and by Zieve, Hill, Hanson, Falcone and Watson in 1951.5 The one-minute value was admittedly arbitrary, but it was supported not only by qualitative observations such as van den Bergh's, but also by time reaction curves, both as previously described 19-21 and as studied in this laboratory. 22 Their character was quite in accord with the presence of two distinct types of bilirubin, a prompt and a delayed, the main period of transition occurring at about one minute. Objection was made to our interpretation of such curves on the grounds that bilirubin in higher concentration does not obey Beer's law, 14, 15 and that similar diphasic curves are observed with certain solutions of pure, crystalline bilirubin.16 However, as pointed out in a later study with Zieve,5 the latter solutions contained CHCl3 which, as Hunter 28 first emphasized, promotes an immediate reaction. Also, it is apparent, if only from comparison of values from various pathologic sera (see below), that striking differences are unaccounted for by the failure to obey Beer's law at the higher concentrations. In the study with Zieve,5 a statistical analysis of a larger amount of data established the significance of the transition from the prompt to the delayed phase of the curves, and supported the one-minute measurement as being the preferable arbitrary point in a range of 30 to 90 seconds. Time curves for representative sera and bile were illustrated in the paper with Zieve and co-workers 5 and need not be reproduced.

The recent studies of Cole, Lathe and Billing 8, 10, 11 have fully confirmed and extended van den Bergh's concept of a fundamental difference between the direct and the indirect reactions. By means of reverse phase chromatography on siliconized Kieselguhr they have separated the direct-reacting bilirubin as a pair of polar pigments differing from chemically pure, free crystalline bilirubin, which is nonpolar in behavior and indistinguishable on their columns from the indirect-reacting serum bilirubin.

Essential confirmation of this work has been noted by Bollman and Mendez,²⁴ although it is of much interest that these investigators find an intermediate type of bilirubin in the blood serum of totally hepatectomized animals. The polar and nonpolar behavior of the direct and indirect type is,

of course, closely related to the relative solubility of the two types in water and chloroform, as already referred to. Dr. Malcolm Campbell in this laboratory has recently found that the prompt direct-reacting type is soluble in glacial acetic acid, the indirect-reacting type relatively insoluble. There is little doubt that this is also correlated with water-solubility, as glacial acetic acid and water are miscible in all proportions, while chloroform and water, of course, are not. Indeed, it now appears that the relative water solubility of the two types may be the basis for all of their differences, including the chromatographic behavior described by Cole and Lathe, also the ready excretion of the prompt direct type in the urine.²²

In the nonpolar, indirect-reacting fraction separated by Cole and Lathe on the siliconized column, no protein was demonstrable. This, of course, does not support the earlier concept that the indirect-reacting serum bilirubin is a bilirubinglobin, as first suggested by Duesberg, ²⁵ later supported by the observations of Fiessinger, Gajdos and Polonovski, ²⁶ and favored in earlier papers by the author. ²² While the possibility is still not excluded that indirect bilirubin as first provided by the catabolism of hemoglobin in vivo is associated with globin, the observations of Cole and Lathe make it clear that such a relationship is unnecessary to the explanation of the indirect reaction. It is necessary to point out that the preliminary treatment used in the Cole-Lathe method might well be expected to dissociate a bilirubinglobin or other protein complex; also, the fact ² that crystalline bilirubin exhibits a direct reaction in 0.01 N NaOH, indirect at 0.001 N, reveals that different factors may be of greater moment under different conditions.

Cole and Lathe's results are in accord with van den Bergh's belief that the prompt direct-reacting bilirubin represents some chemical alteration of the indirect type. They imply a molecular alteration which van den Bergh also favored, rather than a complex with some other substance, such as a bile acid. Others have subsequently favored the latter. Hunter 23 suggested that the prompt direct-reacting bilirubin was simply the sodium salt. was logical insofar as sodium is the principal cation of the bile, and it is true that solutions of crystalline bilirubin in 0.01 NaOH exhibit a prompt direct reaction. The principal objection to this idea is the fact that bile and urine containing bilirubin on standing or heating exhibit a change from prompt direct to delayed or indirect; it is unlikely that a sodium salt would be dissociated in this fashion. Here again one is confronted by the possibility that the prompt direct reaction may be induced by different factors under different circumstances. A striking example of this has recently been afforded in relation to a hitherto undiscovered color reaction of bilirubin, one that we have chosen to designate as the "sulfate" reaction.* Actually, this is a reaction between bilirubin and the Liebermann-Burchard reagent as ordinarily used for the colorimetry of cholesterol. Indeed, the reaction with bilirubin was first discovered some years ago in examining certain residues of bilirubin-

^{*} To be described in more detail in a separate communication.

containing fluids for cholesterol. On addition of the acetic-anhydride-sulfuric acid mixture to a chloroform solution of the residue, an intense dark red color appeared with a strong absorption band at maximum 540 mm. This was also demonstrated with chloroform solutions of pure bilirubin. Quite apart from the possible practical applications of this color reaction, subsequent study has shown what is of greater interest from the standpoint of the fundamental aspects of the van den Bergh reaction, i.e., that when the red chloroform solution is washed with water the original orange-yellow bilirubin color returns and all of the color enters the water phase. The bilirubin is now polar in behavior and exhibits a prompt direct diazo reaction. This is believed to be due to sulfate formation, the acetic anhydride serving only as a suitable vehicle for the sulfuric acid. As far as can be determined, this is the first time that a polar prompt direct-reacting bilirubin has been formed by reaction with an anion at an acid pH in vitro. Although it is unlikely that a bilirubin sulfate is responsible for the prompt direct van den Bergh reaction in vivo, this observation clearly reveals that the formation of a complex with other acid radicals might well explain the polar behavior and prompt direct reaction exhibited by various body fluids. Dr. Rudi Schmid * has very recently obtained important new data indicating that the complexing radical is glucuronic acid.

It is important to bear in mind that free crystalline bilirubin identical in behavior with the nonpolar, indirect-reacting bilirubin of Cole and Lathe has been isolated in relatively good yield from bile, cattle gall-stones, directreacting icteric serum and ascitic fluid, and from human feces.27 Since most of the bilirubin of fresh fistula bile exhibits a prompt direct reaction, 1, 5 it is evident that if this type differs chemically, the change must be easily re-On this basis, at least, it would seem more reasonable that the prompt direct type represents a complex of bilirubin with some other substance or radical. Najjar 28 has suggested that it is a zinc complex, but the evidence for this is inadequate. Dr. Malcolm Campbell and J. B. Carey, Ir., in this laboratory, have recently noted that bile acids are often demonstrable in the polar but not in the nonpolar fractions of the serum bilirubin as obtained by the Cole-Lathe procedures. This is perhaps not surprising, if only on the basis of their water solubility. While the finding does not permit any conclusion as to a possible complex with a bile acid, it at least reveals that a complex of this type with some polar compound must be strongly considered. Schmid's recent evidence, referred to in the foregoing,

indicates that the complex is a glucuronide. (See addendum.)

It is in the cases of pure retention jaundice, such as uncomplicated hemolytic icterus, or the Gilbert type of constitutional hepatic dysfunction, that one finds one of the strongest validations of the fundamental difference between the prompt direct and the delayed direct reactions. As noted in the foregoing, it is this difference which was clearly recognized by van den Bergh

^{*} Personal communication, to be published,

and upon which the later measurement of the 1' bilirubin was primarily based. In following the diazo reaction of serum from such cases, one is impressed by the lack of visible color development within the first few minutes, after which there is a slow, moderate development of color, which may become quite deep on standing for a number of hours. In some instances the majority of the total bilirubin may react in a delayed direct fashion over a period of hours. Often a significant amount reacts within the first 30', the time interval often employed for the direct bilirubin, as proposed by Malloy and Evelyn. As noted in figure 1, the serum from a

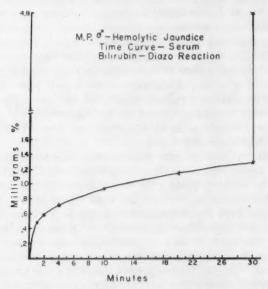


Fig. 1. Time reaction curve of diazo reaction of serum from uncomplicated hemolytic jaundice (M. P., 354, U.H. # 646642). Nonpolar bilirubin from same sample by Cole-Lathe method was less than 5% of total.

case of uncomplicated chronic familial hemolytic jaundice contained a total of 5 mg. of bilirubin, of which but 0.5 mg. reacted within the first minute. At 30', however, 1.3 mg. had reacted. Yet by the Cole-Lathe method applied to this same serum, less than 5% of the bilirubin recovered from the column was polar or "direct" in type. It is evident that the 30' value failed to be as clearly distinctive, and indicated a prominent element of regurgitation jaundice, for which there was no other evidence. Comparisons of 1' and 30' values in cases of hemolytic and other types of jaundice, as in figure 1, have been considered in relation to the results of a study recently reported by Billing.²⁹ Here it is stated that with reverse phase chromatography there was correlation between the polar pigments and the 30' direct bilirubin on the one

hand, and the nonpolar pigments and the indirect on the other, and that no correlation was observed between the 1' readings and either fraction. However, the samples used by Billing in this study were from cases of obstructive or regurgitation jaundice with major proportions of (prompt) direct-reacting bilirubin. It is evident that under these circumstances much larger proportions of prompt direct-reacting bilirubin are lost on the pre-

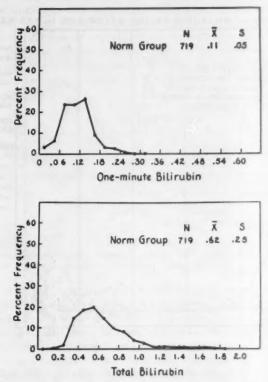


Fig. 2. Normal frequency distribution curves for prompt direct (1') and total serum bilirubins. From Zieve et al., J. Lab. and Clin. Med. 38: 446, 1951. Reproduced by permission of the publishers, C. V. Mosby Co., St. Louis, Mo.

cipitate which is discarded incident to the preliminary treatment of the serum.* Insofar as the total serum bilirubin is concerned, the Cole-Lathe method is in no sense a quantitative differential method, as varying and often large fractions of, more particularly, the prompt direct bilirubin are precipitated and lost, incident to preparing the solution for the reverse phase chromatography. It is believed that the simple time curve of the direct

^{*} Dr. Malcolm Campbell, unpublished.

van den Bergh reaction is probably more reliable in the quantitative separation of the prompt direct from the indirect or delayed direct components. In this connection the character of the curve in figure 1 may be considered. Despite the small amount of prompt direct-reacting bilirubin, there is a definite shoulder at about 1', after which a continuous but much less steep rise occurs to the 30' interval, and at this point, upon the addition of alcohol, the remainder of the bilirubin is seen to react.

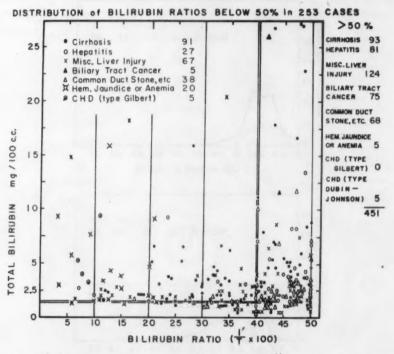


Fig. 3. Plot of total serum bilirubin and bilirubin ratios $(\frac{1'}{T} \times 100)$ in 253 cases with ratios below 50%. The distribution of cases with ratios above 50% is listed at the right. CHD = constitutional hepatic dysfunction; in respect to the Dubin-Johnson disease this designation is purely tentative, with recognition that the cause of the condition is unknown.

Regardless of the fundamental basis of difference between the prompt direct and indirect types, our experience in the last 10 years has increasingly emphasized the clinical value of determining the prompt direct (1'), as well as the total serum bilirubin. Although, as shown in the analysis with Zieve and co-workers, the actual measurement of the 1' prompt direct fraction is slightly less accurate within the normal range, this does not affect the distinction of normal and abnormal values. As may be seen in figure 2, the normal

frequency distribution curve has a sharper cutoff at the higher concentration (0.25 mg./100 c.c.) than does that of the total bilirubin, which shows considerably more tailing, perhaps due to inclusion of mild or borderline cases of constitutional hepatic dysfunction (see below).

During the last 10 years the fractional serum bilirubin determination, 1' and T (total), has been used routinely in the University of Minnesota Hospital and the Minneapolis Veterans Hospital. Some of the earlier data obtained were discussed in a report with Zieve and co-workers. A recent analysis of 889 serum bilirubin determinations from 702 cases serves in part as the basis for the present report. With the exception of the few cases of constitutional hepatic dysfunction, the others in the series were included on a random basis, the only requirement being an elevation of the 1' (> 0.29 mg. %) or of the total bilirubin (> 1.5 mg. %). The material included

TABLE 1
Cases with Total Bilirubin
1.5 or Less, 1' SB > 0.3

Cirrhosis	16	Common duct stone	5
Hepatic carcinomatosis	11	Probably common duct	4
Infections	9	stone Malignancy not involving	4
Hodgkin's disease and leukemia Hepatitis	7	liver or bile ducts	2
Heart failure	6	Carcinoma of ampulla	2
		CD stricture	1
		Pancreatitis	2
		Miscellaneous*	7
		Total	80

^{*} Fatty liver, aplastic anemia, hemolytic anemia, gastrointestinal hemorrhage, duodena ulcer, hemolytic transfusion reaction, periarteritis nodosa, one each.

the abnormal values from the earlier report, analyzed now from a somewhat different point of view, as noted in the following; also, an approximately equal number of cases studied in the last five years, to make the total of 704. The material is subdivided as follows: cirrhosis, 185; hepatitis, 108; miscellaneous liver injury or disease,* 191; extrahepatic cancer of the biliary tract, 80; stone or stricture of the common duct, pancreatitis,* 106; hemolytic anemia or jaundice, 25; constitutional hepatic dysfunction (a) type Gilbert, five; (b) type Dubin-Johnson, five. In cases in which multiple serum bilirubin determinations were recorded, the value with the lowest bilirubin ratio was used in the following analysis, and in the data plotted in figure 3.

The study of these data and the general experience with the serum bilirubin determination during this period have shown that the amount of 1' bilirubin and the proportion of the total that it comprises are of greatest clinical importance in the following respects:

^{*}The miscellaneous liver injury group included heart failure, leukemia and Hodgkin's disease, hepatic carcinomatosis, systemic infections, severe anemia, periarteritis nodosa, chemical poisoning, hemolytic transfusion reactions and other isolated causes. A small minority of cases of pancreatitis are included in the common duct stone or stricture group.

1. Significant increase of the 1' fraction with a normal or slightly increased total bilirubin in which the indirect-reacting fraction (T-1') is within the normal range (< 1.2 mg.). Of the above mentioned 704 cases, 80 were in this category, with subdivision as noted in table 1.

A. Preicteric or anicteric hepatitis. In a report to the College eight years ago, 30 it was pointed out that in cases of infectious hepatitis, either in the preicteric stage or without jaundice at any time, the 1' bilirubin is significantly elevated, at least for a short period of time. Although not included in the present series, many additional examples † have been seen, and it is quite clear that this determination is often helpful in the early detection or distinction of such cases. The elevation is usually accompanied by bilirubinuria, though this is not invariable.

B. Common duct stone without jaundice. Such cases usually present because of pain, chills and fever, or both. The following is a typical example:

J. K., &74. U.H. #869491, April, 1954.

Uncomplicated cholecystectomy, October, 1952. Stones and subacute cholecystitis; apparent uneventful recovery.

Intermittent shaking chills and fever at 10 to 20 day intervals from December, 1952. No pain or jaundice.

Mild rheumatoid disease commencing March, 1953; symptomatic response to cortisone,

Following data during afebrile interval:

Serum bilirubin, 1' 0.5 T 1.2 Ratio 42%

Alkaline phosphatase, 30 K.A. units.

Hemoglobin, 15 gm./100 c.c.; white blood cells, 9400/cu.mm.; 45% neutrophils.

Erythrocyte sedimentation rate, 28 mm./60'

Operation: dilated common duct with many small stones.

Bilirubinuria is often not demonstrable, perhaps because of chronicity and adjustment of the renal threshold at a higher level. In this connection it may be reëmphasized that, in the subsiding stages of infectious hepatitis, bilirubin disappears from the urine at a considerably higher level (0.8–1.2) than that at which it appears in the preicteric stage.³⁰

C. Hepatic carcinomatosis. This is a common cause of elevation of the 1' bilirubin within a normal total. Again, the alkaline phosphatase may be markedly elevated, but the clinical features, and perhaps liver biopsy, usually serve to clarify the diagnosis. The following case is an example:

H. S., & 71. U.H. #824771

Right upper abdominal pain and tenderness, 10 weeks.

Anorexia, weight loss of 30 pounds.

Marked tenderness, right upper quadrant; liver not palpable.

Serum bilirubin, 1' 0.5 T 1.0; urine bilirubin +.

Laparotomy: diffuse hepatic carcinomatosis.

†The majority of these have been observed outside of the University or Veterans Hospitals and are not included in the 108 cases of hepatitis listed above; most of the latter were studied in the icteric or subsiding stages of the disease.

D. Cirrhosis of the liver. A fair number of cases present without jaundice and without elevation of the total serum bilirubin, yet the 1' fraction is significantly increased, often two to four times the upper range of normal. This has been observed in certain instances in which the clinical and laboratory features were more suggestive of the cholangiolitic type—in other words, cases without visible jaundice, but with pruritus, relatively normal hepatocellular function, but increased serum cholesterol, alkaline phosphatase and bile acids. An example is given in the following:

A. T., 964. U.H. #808245

Back pain, bloating, pruritus, one year.

Recent hematemesis.

Xanthelasma, liver enlarged 8 cm. below costal margin in midelavicular line.

Serum bilirubin, 1' 0.5 T 0.7. Urine bilirubin, 0.

Serum bile acids (cholate), 6.8 mg./100 c.c.; control, 0.9 mg./100 c.c.

Cephalin flocculation 0; thymol turbidity, 16; zinc turbidity, 17.

Serum proteins, 6.6 (A 2.7)

Total cholesterol, 237 mg./100 c.c.; 65% esters.

Bromsulphalein retention 44%/45'.

Cholangiogram (local anesthesia, through gall-bladder), normal.

Liver biopsy: portal (non-fatty) cirrhosis.

In many cases of cirrhosis, however, the elevation of 1' bilirubin is, of course, accompanied by much more evidence of hepatocellular functional impairment than in the above instance.

In all of the above situations the determination of the 1' bilirubin fraction has considerably enhanced the general value of the serum bilirubin determination, as it has shown abnormality where determination of the total bilirubin alone would have failed to do so.

2. Retention jaundice. Elevation of the total bilirubin due in the main

or wholly to the indirect or delayed reacting type.

Although retention jaundice is most characteristic of hemolytic disease, it is well recognized that it may also occur because of diminished hepatocellular function of various origin. Van den Bergh recognized that cardiac jaundice was at times of this type. The older studies of Maugeri ³¹ and Eppinger ³² leave little doubt that many of these cases have increased bilirubin production. Whether due simply to passive congestion of lungs, liver and spleen, or to passive congestion plus pulmonary infarction, there can be little doubt that this, together with decreased liver cell function, readily produces retention jaundice. There are also many cases of cardiac jaundice in which there is variable increase of the prompt direct reacting bilirubin as well. Van den Bergh believed that this was due to inspissation of bile with intrahepatic obstruction, but it is also not unlikely that humoral factors are responsible for cholangiolar injury and resultant leakage of bile into the lymph and blood.

A relatively pure retention jaundice is observed at times in the subsiding

or convalescent phase of infectious hepatitis. When this appears to be static, or persists indefinitely unaccompanied by other evidence of liver functional impairment, one must ask whether the patient did not have a constitutional hepatic dysfunction of the Gilbert type to which the acute hepatitis was simply added as a coincidental disease. Several unquestionable examples of this have been studied. Nevertheless, there are cases of hepatitis in which it appears that there is a relatively slow return of hepatocellular function to normal, a mild retention jaundice being present and disappearing gradually over a period of months. An unusual example of mild relapsing hepatitis with retention jaundice is given in the following:

W. B. 40, U.H. #764926

Aug. 1944. Epidemic hepatitis. Apparent recovery.

Nov. 1945. Similar episode, light stools, dark urine, tender liver.

Apr. 1946. Similar episode.

Apr. 30, 1946. Liver edge 4 cm. below costal margin. Serum bilirubin, 1' 0.2,
T 2.8; ratio, 7%. Urine Ehrlich: 1.9-2.1 units/2 hrs. (×3). Bromsulphalein retention, 5%/45'. Cephalin flocculation, trace. Thymol turbidity, 2. Feces Ehrlich: 160 units/100 gm. Reticulocytes, 2.1%.

It is of special interest to contrast the fractional serum bilirubin data in the two types of constitutional hepatic dysfunction, that of Gilbert and that of Dubin and Johnson,³⁸ as seen in table 2. The latter form is also clearly distinguished by the prominence of a brown pigment throughout the

Table 2

Contrast in Fractional Serum Bilirubins in the Two Types of Constitutional* Hepatic Dysfunction (Gilbert or Dubin and Johnson)

Gilbert	1'	T	Ratio %
Case 1	0.96	8.8	11
2	0.38	5.25	7.2
3	0.32	4.0	8.0
4	0.3	3.6	9.0
. 5	0.2	1.7	11.8
Dubin-Johnson			
Case 1	3.8	6.4	59.3
2	2.4	5.6	43
3	5.1	8.6	59
4	1.8	3.6	50
5	1.0	3.3	30

^{*} See legend, figure 3.

liver, while in the former the histology is normal. The striking differences in serum bilirubin partition in these two conditions alone provide convincing evidence of the validity of van den Bergh's concept, and the value of the fractional determination.

It is interesting that when some cause of liver injury promoting regurgitation jaundice is superimposed upon a previous Gilbert type of constitutional hepatic dysfunction, the bilirubin ratio may change remarkably even though the total bilirubin may decline. This is seen in the following:

E. K., Q 52. U.H. #753641

1945. Long history of intermittent mild jaundice. Physical findings normal except old rheumatic mitral and aortic valve defects without heart failure. Serum bilirubin, 1' 0.38, T 5.25. Cephalin flocculation, thymol turbidity, bromsulphalein retention, urine urobilinogen, all normal.

1951. Congestive heart failure. Serum bilirubin, 1' 1.0 T 2.8. Cephalin flocculation, 2+. Bromsulphalein retention, 28%/45', urine urobilingen, 14.8

mg./d.

This seeming paradox represents an intriguing problem which is not at all clear, yet the findings are of obvious significance.

3. Regurgitation jaundice.

This term has usually been employed to indicate a return of bile to lymph and blood, due to cholangiolar injury. It is fully recognized, however, that at least under some circumstances the term may relate simply to a reversal of direction of biliary elements such as prompt reacting bilirubin, from liver cell to lymph and blood, rather than to bile capillary. This would imply that change from indirect to prompt direct bilirubin may occur in the liver cell without mediation of the bile itself. Such a mechanism would seem more reasonable in high grade or complete biliary obstruction in which there is cessation of bile flow.

Because the fractional serum bilirubin determination commonly fails to distinguish between parenchymal and extrahepatic or mechanical causes of regurgitation jaundice, the thought has often been expressed that it has insignificant value and that measurement of the total bilirubin suffices. It is scarcely surprising that one often finds relatively high percentages of prompt reacting bilirubin in many cases of parenchymal jaundice, such as hepatitis and cirrhosis. This may reasonably be ascribed to intrahepatic cholangiolar disturbance, whether it be on the basis of increased permeability with leakage of bile into the adjacent lymph spaces and thence into the blood, or on the basis of intrahepatic obstruction due to edema, swelling of cells, bile thrombi or hemorrhage, and disorganization secondary to necrosis. We have favored the former factor because of the frequency with which regurgitation jaundice is encountered in cases with long-standing hepatitis having remarkably good liver cell function and surprisingly little histologic evidence of abnormality.33 These are the so-called pure cholangiolitic cases, but it should be emphasized that in many others—in fact, in the majority of cases of parenchymal jaundice—there is also evidence in varying degree of hepatocellular functional impairment. At the same time, one often finds elements of the bile in the circulating blood in increased amount, such as bile acids and alkaline phosphatase, together with prompt direct reacting bilirubin. Thus it would be anticipated that a van den Bergh reaction with a considerable proportion of prompt reacting bilirubin might occur with such frequency in the parenchymal types of regurgitation jaundice that the fractional serum bilirubin determination would have relatively little diagnostic value in these cases. Nevertheless, one would also anticipate some borderline percentage of the prompt direct reaction below which the likelihood of parenchymal-hemolytic or hemolytic disease would be increased to such an extent that the ratio would now be of distinct value in differentiation. The earlier study with Zieve and associates 5 showed that a significant proportion of cases of cirrhosis of the liver stand out quite clearly by virtue of a bilirubin

ratio $(\frac{1}{2} \times 100)$ below 40. The more extensive analysis of the present

study reëmphasizes the relative frequency with which such ratios are encountered in cirrhosis, at the same time showing that other forms of liver dysfunction or liver disease are more likely to exhibit low ratios than is true of extrahepatic biliary obstruction. In figure 3 data are plotted only for those cases in the total series in which the ratio was 50% or below. Since it is clear that ratios above 50% are of no significance in distinguishing parenchymal from obstructive causes of regurgitation jaundice, they have been excluded in figure 3. It is apparent that there is a significant preponderance of the parenchymal group below 50%.

It is seen that about half of the cases of cirrhosis have ratios of less than 50% while 75 out of 80 of the biliary tract cancer group have ratios greater than 50%. On the other hand, about three fourths of the total hepatitis group also have ratios above 50%. The majority of the miscellaneous liver injury group likewise have higher ratios. Except that biliary tract cancer is unlikely with ratios below 50%, this dividing line is of little help as far as regurgitation jaundice is concerned. It is noteworthy that there were five cases of hemolytic jaundice with ratios above 50%, due in all instances to obvious hepatic injury, as with severe transfusion reactions, chemicals or infectious factors.

In accordance with earlier experience, 5, 15b, 18 an outspoken difference in figure 3 is first encountered below 40%. Ratios below 35% are limited with but five exceptions to the parenchymal-hemolytic group. It is noteworthy that all of these five are in cases of common duct stone or other benign biliary tract disturbance, and that the elevations are borderline, for the most part being due entirely to increase of the 1' fraction within a normal, or at most slightly increased total. This is also true of most of the cases of the biliary tract groups having ratios from 35 to 40%. Thus, if one excludes from consideration values in which the total bilirubin is normal (1.5 or below), a considerable segment remains which is represented almost solely by cases in the parenchymal-hemolytic groups. This segment, in figure 3, is outlined by a double line. While it is evident that cirrhosis is much more frequent in this segment, there are also cases of hepatitis and other forms of parenchymal liver injury, such as passive congestion, Hodgkin's disease, carcinomatosis and others.

It is well known that there are cases of infectious hepatitis with a hemolytic component. In such instances it would be expected that the bilirubin ratio would be low. The following is an example:

R. J., & 63. U.H. #642020. Infectious hepatitis with hemolytic anemia.

Jaundice of 4 weeks' duration. History of contact. Anemia, hepatosplenomegaly; liver biopsy: hepatitis.

Hemoglobin, 9.5 gm.; MCV, 118; MCC, 33%. Reticulocytes, 14-30%.

Direct Coombs' + Fecal urobilinogen 1,166 mg./d.

Date	6-10	6-21	6-22	6-29	7-28	10-6
SB 1'	4.2	2.9	3.0	2.3	0.1	0.1
SB T	10.0	7.1	6.9	5.7	3.1	0.95
Ratios%	42	40	43	40	3	10

Improvement on cortisone; gradual recovery.

An example of hepatic cirrhosis with relatively low bilirubin ratio despite deep jaundice is given in the following:

F. B., & 49. U. H. #870240. May 1954.

Weakness, anorexia, light stools for six months.

Marked jaundice, spider nevi, ascites; liver and spleen palpable.

Serum bilirubin, 1' 5.3, T 15.8; ratio, 33%.

Cephalin flocculation, 4+; thymol turbidity, 12; total proteins, 6.0 (A 1.8 Died. Necropsy revealed "post necrotic" cirrhosis. (G. 4.2

It seems not unlikely that in many of the cases of cirrhosis or hepatitis with bilirubin ratios of less than 45, increased hemolytic activity may be present and should be sought at least by means of reticulocyte and fecal urobilinogen determinations.

From the standpoint of distinguishing parenchymal and/or hemolytic causes of jaundice on the one hand from extrahepatic or obstructive causes on the other, experience indicates that when the total bilirubin is elevated (>1.5) and the bilirubin ratio less than 40%, there is small likelihood of an extrahepatic obstructive cause and almost none when the ratio is below 35%.

SUMMARY AND CONCLUSIONS

1. The original observations of van den Bergh on the essential difference between the prompt direct and the delayed or indirect reacting fractions of the serum bilirubin are fully supported by recent observations, especially those of Cole and Lathe on the polar, or water soluble, and nonpolar, or water insoluble, character of the two types. The hitherto undescribed bilirubin sulfate is a polar compound exhibiting a prompt direct diazo reaction. The ease with which nonpolar, crystalline bilirubin can be isolated from sources such as bile, in which the initial behavior is almost entirely polar, is more in accord with a complex than an intrinsic molecular difference.

2. Additional emphasis is justified as to the validity of measurement of the direct reacting bilirubin at one minute. Measurement at 30' includes significant fractions of the delayed, indirect or nonpolar bilirubin. This is well demonstrated when the values at 1', 30' and the total (after alcohol), obtained with serum from cases of uncomplicated hemolytic jaundice, are

compared with the amounts of polar and nonpolar bilirubin from the same samples, separated by reverse phase chromatography. The correspondence between 1' and polar bilirubin is excellent. The 30' direct bilirubin, however, clearly includes nonpolar bilirubin.

3. The accumulated experience with the determination of 1' and total bilirubin, and bilirubin ratio, in the past 10 years in relation to the clinical problems of jaundice, liver and biliary tract disease, and anemia, has fully confirmed the usefulness of this fractionation and the manner in which it often enhances the value of the serum bilirubin determination. The latter may be summarized as follows:

A. The 1' bilirubin is often increased significantly within a normal value for total bilirubin. This has been observed especially in cases of early hepatitis, cirrhosis, common duct stone and hepatic carcinomatosis. The finding is of value in revealing an abnormality and, while not differential in itself, often points to the presence of disease of the liver or biliary tract.

B. Low bilirubin ratios in cases with elevated total serum bilirubin are indicative of retention jaundice in varying degree. The lowest ratios (<20%) are characteristic of hemolytic disease or constitutional hepatic dysfunction of the Gilbert type. The Dubin-Johnson type of jaundice and hepatic dysfunction generally exhibits ratios above 40%, most often in the range characteristic of ordinary regurgitation jaundice.

C. While the majority of patients with jaundice due to parenchymal liver disease have bilirubin ratios in the same general range as found in cases of biliary obstruction (45 to 80%), there is a significant segment of cases with diffuse liver disease in which ratios below 40% are encountered. In the range of 35 to 40% there is small likelihood of confusion with (benign) biliary obstruction, and below 35% almost none.

ADDENDUM

Since submission of the above for publication, a study by Billing and Lathe has appeared which, like Schmid's study, referred to in the foregoing, demonstrates that the polar bilirubin of bile and obstructive jaundice serum is a glucuronide.³⁵

This report antedated the publication of Schmid's study, which recently appeared.36

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SUMMARIO IN INTERLINGUA

Recente observationes del character polar e nonpolar del bilirubinas a reaction prompte directe e a reaction retardate o indirecte, respectivemente, supporta plenmente le conclusiones original de van den Bergh in re le differentia essential inter le duo typos. Le character polar del typo prompte directe es possibilemente le resultato de un complexation con un molecula aqua-solubile, secundo le typo de un non previemente describite sulfato de bilirubina. Bilirubina e acido sulfuric, sub conditiones appropriate, produce un reaction de color rubie in le absentia de aqua. Post le addition de aqua, le color original de bilirubina retorna, sed su comportamento es nunc polar, e le diazo-reaction es de character prompte directe. Recente observationes independente per Schmid e per Lathe e Billing indica que un glucuronido

de bilirubina es possibilemente responsabile pro le comportamento polar e le diazoreaction prompte directe de bile e de sero sanguinee ab patientes con jalnessa de

regurgitation.

Le mesuration de bilirubina a reaction directe post 30 minutes include variabile fractiones del retardate o indirecte o nonpolar bilirubina, durante que le fraction directe post 1 minuta es integremente polar. Experientias additional in le determination de bilirubina post 1 minuta e de bilirubina total e del proportiones bilirubinic, basate super un serie de 889 determinationes in 702 casos in que il habeva un certe elevation in un o ambe fractiones, revela que le mesuration del fraction directe post 1 minuta meliora le valor del determination de bilirubina seral in le sequente manieras: (a) Augmentos de bilirubina post 1 minuta in le presentia de constante normal valores total es frequentemente observate in casos de calculo de ducto commun, etiam in cirrhosis e carcinomatosis hepatic, e in certe altere conditiones. Ben que non de valor differential per se, le phenomeno revela un anormalitate e suggere le presentia de lesion hepatic o morbo del via biliari. (b) Proportiones bilirubinic de infra 35% es clarmente un indication de jalnessa parenchymal o hemolytic o de un combination del duo. Le plus basse proportiones (infra 20%) es characteristic de morbo hemolytic o del typo Gilbert de dysfunction hepatic constitutional. In le presentia de proportiones de inter 35 e 40%, il ha un forte preponderantia del gruppo parenchymal-hemolytic. Valores supra 40% non es distinctive. Le typo Dubin-Johnson de jalnessa idiopathic (constitutional) exhibi proportiones de supra 40%, per contrasto con le typo Gilbert de dysfunction hepatic.

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SERUM HEPATITIS FOLLOWING DENTAL PRO-CEDURES: A PRESENTATION OF 15 CASES, INCLUDING THREE FATALITIES*

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Homologous serum hepatitis occurring after administration of blood, plasma and certain derivatives has been well documented and is considered a calculated risk. In recent years another source of serum hepatitis has been recognized. It occurs after the skin has been punctured for therapeutic, diagnostic or cosmetic reasons. Epidemiologic studies of needle or syringe hepatitis are infrequent except for sporadic reports indicating that transmission has occurred in diabetic clinics, syphilitic clinics, among narcotic addicts,8 and during tattooing 4 and other procedures involving skin penetration.5,6 Apparently persons in the prodromal stage of serum hepatitis, or those with a subclinical infection, can be the source of the infective material. Probably, however, the primary reservoirs of serum hepatitis are asymptomatic carriers of the virus. 7, 8, 9 The supposition is that the virus is deposited in needles and syringes and that, because of improper sterilization, the virus remains viable and is transmitted to the next susceptible individual exposed to a skin puncture with the same instrument. Both Neefe 10 and Murray 11 have recently published excellent articles on the whole subject of viral hepatitis, and they should be consulted for details not within the scope of this paper.

It is our purpose to call attention to an apparently not infrequent cause of hepatitis. In 1952 members of the house staff at this hospital first became aware of the appearance of hepatitis following dental procedures. Since this form of hepatitis is preventable, the medical and dental professions should be alerted to the problem. There is only one previous report in the American literature which seems to suggest such a relationship. However, on the basis of the data presented it is difficult to see how this relationship was established.

MATERIAL

This study extends over a two-year period, from June 1, 1953, to May 31, 1955. All patients discharged from the medical service of the Rochester General Hospital during this period with the diagnosis of infectious hepatitis or serum hepatitis are included. All data were taken from the charts. Ex-

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cluded were five cases of hepatitis due to infectious mononucleosis as proved by a rising heterophil titer. Fifty-seven cases of viral hepatitis remained for study. Of these, seven cases were serum hepatitis following blood or plasma transfusion. The remaining 50 cases ordinarily would have been considered cases of infectious hepatitis. Fifteen of these patients, however, gave a history of a dental injection during the preceding one to six months and will be referred to as the dental serum hepatitis group.

These dental injections consisted of the injection of procaine during the process of extracting teeth in 13 patients, and the filling of teeth in two patients. One patient in this group also received gas anesthesia and was not absolutely certain about the procaine injection. She did, however, have gum suturing performed at that time. In addition, two of the 15 patients had received penicillin injections at the same time as the procaine injections.

TABLE 1
History Data of 50 Hepatitis Patients

	Hepatitis Contacts		itis Contacts Dental Injections					Other Injections			
	IH	SH	Total	IH	SH	Total	IH	SH	Tota		
Positive Negative	6 17	0 7	6 24	0 16	15 0	15 16	9	2 5	11 23		
No data	12 35	15	20 50	19 35	15	19 50	35	15	16 50		

INFECTIOUS HEPATITIS GROUP

The remaining 35 patients are classified as infectious hepatitis patients. Two of these had also been to a dentist during the preceding one to six months. One had had her teeth cleaned, and the other had had a filling without any injection. Out of these 35 patients, 16 had a negative dental injection history recorded, and 19 had no data pertaining to any dental visits. Eighteen patients had a negative needle history, and nine had a positive history which usually consisted of receiving a penicillin or hormonal injection. Eight had no data recorded as to skin punctures. The same 35 patients gave a positive hepatitis contact history in six cases, negative in 17 and no record in 12 (table 1).

Although 19 records did not specifically mention dental data, and although most of these may have had a negative dental injection history, it is possible that some actually had a positive history. We feel, therefore, that 15 positives out of 50 is a minimal figure. It is our belief that the 15 patients with the positive dental injection history had serum hepatitis which was transmitted at the time of the dental procedures by contaminated needles, syringes or procaine. Other dental instruments and the use of human

thrombin for hemostasis may have been responsible. These 15 patients of the dental serum hepatitis group will be further discussed.

DENTAL SERUM HEPATITIS GROUP (TABLE 2)

Incubation Period: The incubation period, which in our series is defined as the interval from exposure to the appearance of the first symptoms, and not the onset of jaundice, has been calculated as being within certain limits, e.g., plus or minus 15 days (table 2). This was necessary because the date of exposure in most cases was recorded as a certain month. The onset of symptoms was fairly clear in all except one, where it was most insidious. The observed incubation period of all 15 cases falls within the recognized

limit for serum hepatitis, which is approximately 45 to 160 days.

Onset of Illness: The onset of illness in 14 patients was insidious in nature. The remaining patient (case 6—see below) had a rather acute onset. Malaise, fatigue and anorexia, alone or in various combinations, were the first symptoms encountered in 80% of our dental group. Nausea and abdominal ache were next in frequency. One patient initially complained of "gas"; another had backache. Jaundice with anorexia and fatigue was the initial symptom in only one case. The interval from the first symptom to the onset of jaundice was between zero and 18 days. Of the 14 jaundiced patients, nine developed it from one to two weeks after the onset of the illness. Case 11 was admitted toward the end of her illness and at that time was anicteric. Her onset of illness was extremely insidious, with malaise and fatigue one to two months prior to admission. Questionable icterus was noted by her physician one week prior to admission. She had liver tenderness to percussion while in the hospital.

Fever: Only one patient out of 15 had a temperature above 100.2° F. during hospitalization. This patient (case 1) had a temperature of 101.2° F. on admission, 101° F. the next day, and elevations to 100.4° F. for three days. Characteristically, the temperature was at a normal level throughout

the stay for all the others.

Chill: No patient had a chill during hospitalization. One patient (case 6) gave a history of fatigue and malaise on the ninth day prior to admission. This was followed by shaking chills and fever to 103° F. for the next four to five days. He was afebrile on admission and throughout his hospital stay.

Age: In age, the patients were equally distributed from 18 to 71 (table

2). Ten of the 15 patients were above the age of 30.

Laboratory Data: The admission laboratory data of the 15 dental serum hepatitis patients are characteristic of hepatitis (table 2). Repeat studies during their hospital stay were in keeping with those observed in viral hepatitis.

Mortality: This series includes three fatalities, all in the dental serum hepatitis group. We present briefly these fatal cases and one average case.

Table 2
Fifteen Cases of Serum Hepatitis Following Dental Procedures
Admission Laboratory Data

	Glob. 14-24 (gm. %)	2.1	v	00			2.0		5.3	2.1	1	2.5	000	2	3.9	
Protein	Alb. 4-6 (gm. %)	4.8	4.0	2.4	21.		3.0		W.	4.0	4.6	44	2.7		4.2	
	Tot. 6-8 (gm. %)	6.9	W.	6.3			5.0		8.9	6.1	6.1	9.9	ur,		7.2	1
terol	Ester (60-150 mg. %)	The state of the s				33	72		36	35	31	338	34	78	09	30
Cholesterol	Tot. (150-250 mg. %)					137	152		165	137	142	166	166	195	186	733
Bilir, Tot.	(0.1–1.0 mg. %)	9.6				6.9	6.3	8.2	18.3		5.6	0.8	29.0	7.2	15.4	0 +0
Icteric	Index (4–6)	75	156	150	56	35	22	34	80	89	30	9	138	28	500	00
Alkaline	Phos. (1.5-4.0 Bod. U.)	5.3	3.4		2.4	4.8	1.3	8.6	3,3	5.0	3.5	1.2	4.5	4.3	4.1	4 4
Thymol	Turb. (0-4u)	18.4			16.6	15.6	26	10	22	15.2	10.4		8.0	19	18	3.5
Cephalin	Floc. (neg2+)	3+		++	3+	3+	++	++	++	4+	4+	3+	++	++	++	1 1
Incubation	Period in Days	86± 5	98±15	47±15	51±15	119± 3	102	102±15	123±15	68 ± 15	87±15	116±35	123±15	142±15	78±15	00 1 2
	Age	28	56	56	18	27	35	52	09	46	41	24	7.1	41	63	20
-	5	M	-	M	M	M	M	M	(I	H	1	(2.	M	(x	(+,	N.A.
	Case	1	7	23	+	2	9	1	00	6	10	11	12	13	14	1 5

CASE REPORTS

Case 2. This 56 year old housewife was admitted to Rochester General Hospital on June 26, 1953. At this time she was already in hepatic coma after a three-week history of progressive fatigue, malaise and anorexia, which after one week had been followed by jaundice. The patient had been treated at home. Two days before admission she started to have nausea and vomiting and became agitated. She had had extraction of teeth with procaine and penicillin injection four months before admission.

Physical Examination: The patient was semicomatose, thrashing around in bed and deeply jaundiced. Blood pressure was 100/80 mm. of Hg; pulse, 68; temperature, 97.8° F. The liver was described as being enlarged to four fingerbreadths

below the costal margin and markedly tender!

Laboratory Data: Hemoglobin, 14 gm.; red blood cells, 4,040,000; white blood cells, 11,100, with a differential of 86% neutrophils, 13% lymphocytes and 1% monocytes. The hematocrit was 42%. Blood sugar, 55 mg.%. Icteric index, 156. Alkaline phosphatase, 3.4 Bodansky units.

Hospital Course: The patient received the usual supportive therapy and was placed on cortisone. She did not respond to therapy and died on the third hospital

dav.

Necropsy Report: Gross pathology revealed an extremely jaundiced, well nourished and well developed female. The liver was 3 cm. above the right costal margin. The left lobe was just visible beneath the xiphoid process. The liver weighed 750 gm. and was very flabby. Its capsular surface was somewhat opaque and a grayish green. The free margins were somewhat rounded. The cut surface was a variegated yellow-red, with the yellow predominating. A slight lobular pattern was visible; in some areas this even had an appearance similar to that of the so-called "nutmeg" liver. The spleen weighed 120 gm. The gall-bladder contained no stones. The

extrahepatic biliary passages were patent.

Microscopic Examination: The lobular structure of the liver was hyperexaggerated, due to areas of hemorrhagic necrosis in almost every lobule. Almost everywhere the portal areas were spared, but with this exception: almost any part, central, mid, nearportal or the lobule, might be the site of the necrosis. The remaining liver cells were markedly altered. They were larger than usual, often twice the usual size, and somewhat disarranged; cord structure was especially difficult to make out. The nuclei were somewhat hyperchromatic; there were often two nuclei in a single cell and, not rarely, several. The cytoplasm near the nucleus was generally dense and granular, but in the periphery of the cell it was vacuolated or foamy; occasionally the whole of the cytoplasm was foamy. Bile canaliculi could not be made out, and there were no bile thrombi. A few liver cells lying at the junction of necrotic and intact zones contained bile pigment in the cytoplasm. There were a few inflammatory cells in the portal areas. Fibrosis was minimal. Bile ductules, on the other hand, were moderately proliferated.

Pathologic Diagnosis: 1. Diffuse subacute necrosis of the liver with regeneration.

Comment: The final interpretation was that this patient had a severe serum hepatitis producing an acute necrosis of the liver.

Case 8. A 60 year old housewife was admitted to the Rochester General Hospital on September 21, 1954, with a history of yellow skin for two days. On September 16 she had had a feeling of much "gas" in her abdomen. The next day her stools were light yellow, but her urine had been darker for one week. She had no nausea, vomiting, pain, fever or chills. In May, 1954, she had had a tooth extracted with procaine injection. She had had no contact with hepatitis or with jaundiced

individuals. One week prior to admission she had had a fulguration of a small skin lesion.

Physical Examination: Her skin and sclerae were icteric. The blood pressure was 140/74 mm. of Hg; pulse, 84; temperature, 99.2° F. The liver was palpable 3 cm. below the costal margin. The spleen was not palpable.

Laboratory Data: On admission complete blood count, hematocrit, fasting blood sugar, nonprotein nitrogen and prothrombin time were normal. The other data are presented in table 2.

Hospital Course: The patient was put at bed-rest, with a high protein, high carbohydrate diet. She remained afebrile and had an uneventful hospital course. She was discharged on October 21, 1954, the thirty-first hospital day, for further therapy at home. At this time her chemistry revealed a cephalin flocculation of 4 plus, thymol turbidity of 11.2, and an icteric index of 16.

Case 12. A 71 year old married chiropractor was admitted to the Rochester General Hospital on January 2, 1955, with a history of jaundice for 10 days. The onset of illness was insidious, with appearance of an achy pain in his left upper back with radiation to the left shoulder four weeks prior to admission. With the appearance of jaundice his urine became darker and stools lighter. Anorexia was present, and food was tasteless to him. There was no nausea, vomiting, food intolerance or diarrhea. He had lost eight pounds in three weeks. He gave a history of having had seven teeth extracted with procaine injection during the first week of August, 1954. He had had no contact with hepatitis.

Physical Examination: The patient was markedly jaundiced. Temperature was 99.2° F.; pulse, 68; respiration, 16; blood pressure, 110/60 mm. of Hg. The liver was palpable three fingerbreadths below the costal margin and was slightly tender.

Laboratory Data: On admission the patient had normal complete blood count, blood urea nitrogen, fasting blood sugar and prothrombin time. The other admission data are presented in table 2. Ten days after admission he was found to have a normal blood lipase and amylase.

Hospital Course: The patient received the usual supportive therapy but his condition became worse. Cortisone was started on January 9, 1955. He was afebrile throughout his hospital course. The stool was negative for bile on January 13 and did not become positive until January 27. His icteric index increased to 165 but had come down to 99 by February 4, 1955. The alkaline phosphatase continued at a normal level, whereas the thymol turbidity and cephalin flocculation remained elevated. The prothrombin time declined to 60% (patient, 37 seconds; control, 22 seconds), and elevation of blood sugar and blood urea nitrogen was noted. Mental changes became evident, and lethargy was present for several weeks. He died on February 16, 1955, his forty-sixth hospital day.

Necropsy Report: Gross pathology revealed a markedly jaundiced elderly male. The abdominal cavity contained 4 L. of amber fluid. The liver was small, green and high up underneath the ribs, and weighed 1050 gm. The surface was finely nodular and a dark brownish green. On section it was greenish and lobulated, with a "nutmeg" appearance, except that it was green and yellow. It was much firmer than usual, and held its shape both before and after sectioning. It was similar throughout. The gall-bladder contained no stones. The extrahepatic biliary passages were patent and of normal size and appearance. The spleen weighed 200 gm. The pancreas was of normal size. Extensive fat necrosis was present.

Microscopic Examination: There were widespread areas in which liver parenchymal cells had been destroyed and replaced by large masses of connective tissue. This connective tissue appeared to be largely in portal areas. It formed irregular branching bundles which in some places occupied central zones. In these areas there was a marked increase in the number of bile ducts, apparently due to prolifera-

tion of the ducts. The latter were filled with inspissated masses of bile, as were the smaller terminal bile canaliculi. There was a moderate infiltration of lymphocytes in the portal areas. Some macrophages containing bile were also present. There were focal areas of cellular necrosis, chiefly central. The liver cells were swollen and filled with bile pigment, and showed some fragmentation. This was predominantly central. Many of the surviving liver cells were in rounded and irregular masses without lobular arrangement.

Pathologic Diagnosis: 1. Diffuse subacute necrosis of the liver. 2. Chronic

pancreatitis with fat necrosis.

Comment: This patient had serum hepatitis with severe liver damage, resulting in complete nonfunctioning for a period of time, but some recovery took place prior to his death.

Case 15. This 38 year old married white knife-grinder was admitted to the Rochester General Hospital on March 27, 1955, with a history of fatigue, anorexia and malaise for two weeks. He had noted jaundice three days before, and his stools had become lighter and urine darker. During the first week of December, 1954, he had had a tooth extracted with procaine injection and had received several penicillin injections at this time. He gave a history of having drunk five to six glasses of beer daily for 15 to 20 years, and also admitted to drinking some wine on occasion.

Physical Examination: Blood pressure, 154/80 mm. of Hg; pulse, 84; respiration, 20; temperature, 99.6° F. Skin and sclerae were icteric. Telangiectases were noted on the upper chest. The liver was palpable 3 to 4 cm. below the costal margin and

was not tender.

Laboratory Data: On admission the white blood count was 13,100, with 90% neutrophils, 1% eosinophils, 1% basophils and 8% lymphocytes. The fasting blood sugar, blood urea nitrogen and hematocrit were normal. The Wassermann examination was negative. The prothrombin time was 55% (patient, 38 seconds; control, 21 seconds), and the stool was negative for bile. The other laboratory data are found in table 2.

Hospital Course: Therapy consisted of bed-rest, a high protein, high carbohydrate, high caloric diet, and intravenous glucose with vitamins and parenteral vitamin K. On April 3, 1955, the patient had a nosebleed and ascites, and a pericardial friction rub became evident. Marked deterioration of his condition prompted institution of therapy with cortisone and vitamin B₁₂. Barium swallow did not demonstrate esophageal varices. Fluid retention increased, and gastrointestinal bleeding was present prior to his death on April 12, 1955, the sixteenth hospital day.

The icteric index had increased to 148.

Necropsy Report: Gross Pathology: A well developed, well nourished, markedly icteric white male. There was a large amount of bloody drainage from the nose and mouth. Multiple purpuric areas were present over the skin. The lungs contained hemorrhagic areas, and bloody fluid ran from the cut bronchi. The abdominal cavity contained 5 to 6 L. of fluid. The spleen weighed 200 gm. The liver weighed 1,730 gm. The surface was nodular and had a definite hobnail appearance. There were some smaller granular nodules also. The posterior surface of the liver had a large nodule about 8 cm. in diameter which was somewhat softer than the remainder and was not covered by the same nodules as in the main part of the liver. The cut surface of the liver was composed of multiple nodules of green tissue which protruded slightly above the cut surface. These nodules were all small, ranging from 0.5 to 1 cm. in diameter. They were separated by fairly thick strands of rather soft, pinkish gray, loose fibrous tissue. These separating strands were not dense and did not feel really scarred; it was fairly soft material. The larger nodule on the under sur-

face of the liver was composed exclusively of the green nodules, with very little of the separating fibrous tissue, and these green nodules were all about the same size but much more closely packed together. The gall-bladder contained no stones. The extrahepatic biliary passages were not obstructed. No tumor was found in the pancreas. There was erosion of the lower part of the esophageal mucosa. Varices were not identifiable. The entire small bowel was filled with dark blood. No bleed-

ing points were found.

Microscopic Examination: There was a well marked, advanced atrophic cirrhosis of the liver. The interlobular periportal connective tissue was very abundant in places, and in it there was marked proliferation of new-formed bile ducts. In a few of the ducts there were bile casts in the lumen. The liver lobules varied considerably in size and shape. Many were large (corresponding to the gross nodular appearances) and were made up of large cells; the appearance was that of a small hepatoma. Two features were present which differed, however, from the usual findings: (1) All the bile canaliculi were easily visible and many were filled with bile "thrombi." Usually this appeared as a thick, somewhat wavy line of olive green, but was intermittently interrupted by larger, spherical clumps of bile. Occasionally the arrangement of liver cells around a large deposit led to a pseudo-alveolar appearance. (2) There were foci of acute liver cell necrosis in the adenomatoid nodules.

Pathologic Diagnosis: 1. Atrophic cirrhosis of the liver. 2. Focal necrosis of liver cells, 3. Gastrointestinal bleeding.

Comment: This patient had a portal cirrhosis resulting in decrease of "liver reserve," but sufficient function to lead a normal life. The superimposed acute hepatitis reduced his liver function further, to a point not compatible with life.

DISCUSSION

We are assuming that infectious hepatitis and serum hepatitis are different entities due to different viruses. This is probable, but not definite. A lack of cross immunity, which points to a different antigenic structure, has been demonstrated, but there is no test for differentiating the two types of viral hepatitis. Serum hepatitis is always diagnosed by history. However, one cannot be definite in any one specific case, since, for instance, it is certainly possible for a post-transfusion patient to come down with infectious hepatitis. The evidence for making a diagnosis of serum hepatitis due to dental work in our 15 cases is certainly sufficient. The incubation period is most significant. Infectious hepatitis can also be transmitted by parenteral means, but the incubation period is shorter.

It is unlikely that such a large percentage of hepatitis patients could have had injections by a dentist just by chance. This points to a definite cause-and-effect relationship. To test this thesis, a control study was undertaken. A total of 79 patients on the medical service of The Rochester General Hospital on December 30, 1955, were interviewed to determine the incidence of dental procedures for the one to six month period prior to admission. Except for nine patients who could not respond to questioning, and two hepatitis cases, 68 were questioned, and the data collected support our sup-

position, since only three patients had a dental injection history. Of interest, too, is the fact that, of the two hepatitis patients excluded, one had had a procaine injection at her dentist's four months before. To evaluate further the incidence of dental injections, a second control group was interviewed. The 50 hepatitis patients were matched by age at random with 50 patients in The Rochester General Hospital on January 23, 1956. Again,

Table 3
Incidence of Dental Procedures in Hospitalized Patients
From One to Six Months Prior to Admission

	Hepatitis Group		Control	Group I	Control Group II		
	No. Pts.	% Pts.	No. Pts.	% Pts.	No. Pts.	% Pts.	
Dental injections Other dental procedures	15	30.0 4.0	3 5	4.4	3 7	6.0	
Negative dental history No dental data	14 19	28.0 38.0	60	88.2	40	80.0	
	50	100	68	100	50	100	

only three patients gave a dental injection history. The incidence of dental injections in our hepatitis group is at least five to seven times as frequent as in our control groups (table 3).

Another factor supporting the relationship of dental injections and hepatitis is the knowledge that a number of these patients had had the same dentist, but exact data are not available.

Suggestive small differences between infectious hepatitis and serum hepatitis exist in groups of patients, but these differences are of much less help in any one case (table 4). We have shown that the clinical picture in

Table 4
Differential Points in Viral Hepatitis

	IH	SH
Incubation period	15-40 days	45-160 days
Type of onset Fever	Acute May be high	Insidious Below 100.2°
Chill	Frequent	Rare
Route Age Mortality	Oral or parenteral Less above 30	Parenteral Any age
Mortality	Very low	Probably higher

our group seems to point more to serum hepatitis as the disease process when consideration is given to type of onset and presence of chill or fever, as well as to age distribution. It is interesting to note that the three fatal cases belonged to the dental serum hepatitis group. This is in keeping with the reported higher mortality in serum hepatitis.

DIAGNOSIS

Establishing the previous dental work is of primary importance in arriving at a prompt probable diagnosis of serum hepatitis, or at least includ-

ing it for consideration in the differential diagnosis. It has been our experience that the usual inquiry about any injections or needles during the last six months will invariably fail to bring out any dental data. Apparently a positive history is rarely obtainable unless specific questions are asked. Our plea, therefore, is that during the history-taking or, better yet, during examination of the patient's oral cavity, he be asked about any visits to a dentist in the last six months, and that this be followed by specific questions as to injections or suturing during these visits.

PREVALENCE

The data presented would indicate that, in this hospital at least, 30% of apparent infectious hepatitis cases in adults actually may be cases of serum hepatitis. At the same time it shows that, out of 22 cases of serum hepatitis over a two-year period, 15 (or 68%) were due to exposure at a dentist's

Table 5
Relative Incidence of Serum Hepatitis and Infectious Hepatitis

	Cases		Percentages	
SH due to transfusions SH due to dental injections Probable infectious hepatitis	7 15 35 57	12.3 26.3 61.4 100	30.0 70.0 100	31.8 68.2

and seven (or 32%) to the actual administration of blood or plasma (table 5). It appears, therefore, that in this community serum hepatitis following dental procedure is a considerable public health problem.

PREVENTION

Chemical sterilization should be abandoned.¹⁴ Autoclaving is a choice method for killing the virus, but of course it must be used properly. Boiling for more than half an hour may be sufficient.

Cleaning of needles and syringes is important. Autoclaving of syringes and needles under conditions of proper moisture, temperature and length of time, and using a different syringe and needle for each patient, may not be enough if the procaine itself has been contaminated.

Since it has been recognized that only 1.0×10^{-4} c.c. of contaminated serum is sufficient to produce serum hepatitis, and since syringe contaminations in several ways have been well demonstrated, the step from syringe to procaine contamination is certainly plausible. If this has occurred, the procaine bottle with its contents can be autoclaved. We suggest that this be done routinely after each procedure in hospital practice, where many different individuals have the opportunity to use one bottle.

SUMMARY AND CONCLUSION

Serum hepatitis has been reported following various skin-penetrating procedures. We have reported 15 cases of serum hepatitis following dental procedure involving mucous membrane penetration. This represented 30% of apparent infectious hepatitis cases hospitalized over a two-year period. Three fatalities occurred in this group.

It has been pointed out that heat sterilization of needles, syringes and instruments is essential to prevent the spread of serum hepatitis. The danger of the use of multiple injection bottles has also been considered.

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SUMMARIO IN INTERLINGUA

Hepatitis a sero homologe, occurrente post le administration de sanguine e de derivatos sanguinee o in consequentia del uso de mal sterilisate agulias e syringas, es ben recognoscite. Le occurrentia de iste morbo post manovras dental ha essite considerate como un possibilitate, sed illo ha nunquam essite documentate. In le presente studio, il esseva trovate que ex 50 casos de apparente hepatitis infectiose vidite in le curso de duo annos, 15 (incluse tres casos mortal) habeva un recente historia de manovras dental, con injectiones de procaina intra le recognoscite periodo de incubation de hepatitis seral. Pro evalutar iste incidentia de 30% de injectiones dental in nostre serie de casos de hepatitis, duo gruppos de controlo esseva interviewate. Pro illos, incidentias de injectiones dental de 4,4 e 6,0% respectivemente esseva constatate. Quando le 15 casos de hepatitis post manovras dental in nostre serie original esseva analysate plus detaliatemente, il esseva trovate que le tableau clinic indica hepatitis seral plus tosto que hepatitis infectiose, viste le typo de declaration, le presentia de algor o febre, e le distribution per etate. Un caso typic e le tres casos mortal es presentate in detalio. Pro iste ultimes, le constatationes autoptic es presentate.

Es ben recognoscite que le principal criterios de differentiation inter hepatitis infectiose e hepatitis seral es fornite per un bon historia del patiente. Proque nos opina que le 15 casos in nostre serie representa hepatitis seral transmittite durante manovras dental, nos sublinea le desiderato de un adequate historia dental in omne patientes con apparente hepatitis. Nostre datos pare indicar que manovras dental—al minus in nostre communitate—es possibilemente un plus importante causa de hepatitis seral que transfusiones de sanguine. Le prevention es possibile per abandonar le sterilisation chimic, per usar adequate methodos de mundation del agulias e syringas, e per evitar cautemente omne forma de contamination via phialas a doses multiple. Sterilisation per autoclave es le methodo de election, ben que ebullition durante un medie hora es possibilemente sufficiente.

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AN INVESTIGATION OF NEUROSURGICAL AL-LEVIATION OF PARKINSONISM, CHOREA, ATHETOSIS AND DYSTONIA *

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INTRODUCTION

It is the purpose of this presentation to summarize the current status and results of a continuing investigation of the neurosurgical treatment of several hyperkinetic disorders that have previously been intractable to medical therapy. Although our investigation has dealt principally with the neurosurgical therapy of far-advanced parkinsonism, it has also included cases of such involuntary movement disorders as chorea, athetosis, and dystonia musculorum deformans. The results achieved to date in each of these hyperkinetic disorders will be presented. For the purpose of this report, details of surgical technic will not be emphasized, but, rather, emphasis will be placed upon rationale of these procedures, results which have been achieved, and the medical and physiologic implications of the results.

It is the thesis of this report that parkinsonism and the other hyperkinetic diseases mentioned above, which have until recent years been considered as hopelessly progressive and irreversible diseases, have now been demonstrated to be reversible by means of neurosurgical intervention. Further, it is proposed that, although the immediate significance of these findings is the fact that certain sufferers from these diseases are now amenable to neurosurgical therapy, nevertheless the medical and physiologic implications of the investigation may, over a longer period, prove to be even more meaningful. It is for this latter reason particularly that I welcomed the invitation to present these results of a surgical investigation to such a distinguished group of medical colleagues.

A REVIEW OF NEUROSURGICAL INVESTIGATIONS IN HYPERKINETIC DISORDERS

The failure of medical therapy to halt the progress of parkinsonian symptomatology and of the usually inexorable course of this disease has led

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neurosurgeons to attempt to devise destructive operations upon the nervous system which might alleviate some of the signs and symptoms of this malady. Similarly, the desperation felt by many of these patients incapacitated by the shaking palsy has led a number of them over the past few decades to be willing to submit to investigative neurosurgical procedures in the hope of obtaining some degree of relief from tremor, rigidity or incapacitation.

During the course of the last 20 years virtually every level of the nervous system has been attacked in pursuit of this goal. In 1937 Bucy ^{1, 2} and Klemme ⁸ introduced operations aimed at resection of part of the premotor cortex of the brain in an attempt to relieve contralateral tremor. These operations invariably resulted in a contralateral hemiplegia, and at times also produced postoperative convulsive seizures. The degree of relief of tremor from such a procedure was proportional to the degree of sacrifice of motor power.

Other neurosurgeons were stimulated by these investigations to attack the pyramidal tract at levels lower than the motor cortex; Putnam ⁴ devised the operation of pyramidotomy in the cervical spinal cord, while Walker ⁵ developed an operation which sacrificed the pyramidal tract at the level of the cerebral peduncle. Each of these operations is capable of relieving contralateral tremor to a degree proportionate to the sacrifice of motor power. Pyramidal tract operations failed to relieve rigidity or incapacitation to any extent and, in fact, often aggravated these symptoms.

Various operations upon the cerebellum, posterior columns of the spinal cord, posterior nerve roots and sympathetic nervous system have been tried for the relief of tremor or rigidity or both, without any appreciable degree of lasting improvement.

In 1942 Meyers introduced a series of experimental operations on the basal ganglia. These consisted of pallidofugal section, either alone or, at times, combined with extirpation of the head of the caudate nucleus, oral half of the putamen, oral pole of the globus pallidus, or section of the anterior limb of the internal capsule. Meyers states that unfortunately the operative mortality attending such operations precludes their general use. However, this investigator demonstrated that, by attacking the basal ganglia, it was possible in some cases to relieve tremor or rigidity, or both, without necessarily sacrificing motor power.

During recent years various surgical technics have been devised in an attempt to achieve some practical operative approach to the basal ganglia in parkinsonism. Spiegel and Wycis ^{11, 12} have produced lesions in the ansa lenticularis by employing a stereotactic apparatus which they developed for operations on the human brain. Narabayashi ¹³ has also attacked the globus pallidus using a stereotactic device, as have others. Thus far, the use of complicated stereotactic apparatus has been confined to investigative procedures and has not yet achieved a practical significance outside of a few teaching centers, which have been able to devote considerable attention to

the development of such instruments. The results achieved, however, are promising, and this approach will doubtless be meritorious as more experience is gained.

Fenelon ¹⁴ has devised a direct method for ansa lenticularis coagulation by passing an electrode directly into the globus pallidus without use of a stereotactic machine. He uses a transfrontal approach, passing his electrode through the tip of the frontal lobe to a depth of 70 to 75 mm. into the brain. Guiot ¹⁵ has also carried out direct coagulation of the globus pallidus and ansa lenticularis by performing a craniotomy and introducing an electrode into the region of the globus by a subfrontal approach. Both Fenelon and Guiot report salutary effects from these procedures.

During the last three and a half years we have carried out two original technics aimed at destruction of the mesial globus pallidus and its afferent connections with other basal ganglia and motor areas of the brain. The first of these is anterior choroidal artery occlusion, which aims at infarcting the mesial globus pallidus by interfering with its blood supply. The second is chemopallidectomy, 19, 20, 21 which aims at the destruction of the mesial globus pallidus by injection of absolute alcohol into this structure. These two technics comprise the investigative approaches used during the course of this study. The results have been increasingly salutary and will be described in detail below.

Several of the procedures mentioned above have also been tried in cases of chorea, athetosis and dystonia musculorum deformans. Promising results have been reported in choreo-athetosis by Spiegel and Wycis, who produced lesions in the globus pallidus stereotactically. Anterolateral cordotomy of Putnam has been employed with some success in lessening athetotic movements, but without encouraging results in dystonia musculorum deformans. Recently, Meyers has performed bilateral crusotomy in certain cases of the latter disease, with reduction of violent movements in certain cases. Our experience with chemopallidectomy in chorea, athetosis and dystonia has been extremely promising and will also be summarized in this report.

MATERIAL AND METHODS OF INVESTIGATION

The clinical material which formed the basis of this investigation is comprised of 200 operations in cases of far advanced, hyperkinetic disorder. Of these 180 operations were performed in patients who manifested the syndrome of parkinsonism. The remaining 20 were carried out in cases of various other hyperkinetic disorders, which could be grouped as chorea, choreo-athetosis, tension-athetosis, and dystonia musculorum deformans. Thus a total of 200 operations, the aim of which was to destroy a portion of the globus pallidus, were performed in this group of patients. Fifty-five of these operations were surgical occlusion of the anterior choroidal artery. One hundred forty-five of the operations were chemopallidectomy.

The rationale of the procedure of anterior choroidal artery occlusion is that, by occluding the anterior choroidal artery, one often infarcts the mesial portion of the globus pallidus and certain of its extrapyramidal neural connections. Prior to operation a cerebral arteriogram is performed in order to visualize this vessel and to make the surgical approach more facile technically. A small subtemporal craniectomy is performed, usually under local anesthesia. The temporal lobe is elevated, exposing the contents of the basilar cisterns, namely, the oculomotor nerve, the internal carotid artery and its posterior communicating and anterior choroidal branches. The latter vessel is occluded by electrocoagulation with a unipolar current. Technical details of this procedure are described in earlier communications.

The operation of chemopallidectomy involves the placing of a small polyethylene catheter through a trephine opening in the skull into the mesial globus pallidus. The procedure can be carried out simply under x-ray control, with little or no special instrumentation. When the end of the catheter has been placed in the region of the globus pallidus, .25 c.c. of procaine is injected intracerebrally. If the catheter has been correctly placed, tremor and rigidity of the contralateral extremities are almost instantaneously alleviated. This simple intracerebral "nerve block" identifies a physiologic landmark, the destruction of which will produce lasting alleviation of contralateral tremor and rigidity. We carry out destruction of this region by injection of .5 to 1 c.c. of Ethocel, a solution of 8% celloidin in 95% ethanol.* Technical details of this procedure have been previously reported and require no further elaboration here.

A detailed system of evaluation and appraisal of each patient prior to operation and at various follow-up periods after surgery has been used during the course of this investigation. A team of examiners, consisting of four physicians, two medical psychologists, physiotherapy technicians, speech therapists, and nursing attendants subjects every patient undergoing operation to a thorough physical examination, a neurologic examination, a series of practical tests of the activities of daily living, psychologic studies

and speech evaluation.

Electromyographic and cinematographic records also constitute part of the regular work-up. Motion picture studies of each patient in this series are made preoperatively and at frequent intervals postoperatively. The patient's subjective impressions, as well as objective appraisals by the relatives, nurses, attendants and the referring medical doctors, have been made permanent parts of each patient's record.

RESULTS OF ANTERIOR CHOROIDAL ARTERY OCCLUSION IN PARKINSONISM

The operation of anterior choroidal artery occlusion has relieved contralateral tremor, rigidity, and/or other components of the syndrome of

^{*}Ethocel was supplied to us by Dr. John Saunders, of Ciba Pharmaceutical Company.

parkinsonism in 70% of the 55 times it was carried out in this series of cases. These results have been achieved in cases which were of long standing, far advanced and usually greatly disabled. Reference will be made to the effect of this operation on the individual abnormalities of the parkinsonian syndrome.

Tremor: Resting tremor which is confined to the distal portion of the extremities has been virtually abolished in the extremities contralateral to the occluded artery in 65% of our cases. This relief of tremor has not entailed any compromise of motor function. In successful cases alleviation of tremor was evident immediately following operation and has persisted to the present time. The several instances in which relief of tremor was transient are included statistically among the unsatisfactory results. Tremor which persists through motion, as an intention tremor, is ordinarily not alleviated by operation. Major tremor which shakes the entire extremity vigorously, thus causing shaking of the neck and trunk as well, is usually not completely alleviated. However, among the patients whose resting tremor was noted to be completely obliterated were several in whom the tremor had been rated grade 4 (most severe) prior to operation.

Rigidity: Rigidity has been lessened in 75% of the cases of successful occlusion of the anterior choroidal artery. In many of these, cogwheelism and resistance to passive movement disappeared completely. Increased usefulness of the extremities was noted immediately in these cases. The relief of rigidity is, in fact, the most constant favorable effect of operation.

Gait: A number of patients have demonstrated a marked improvement in gait. Among these are several who were bedridden before operation but are now able to walk well without aid. Propulsion and retropulsion have disappeared in some instances.

Motor Power: Hemiplegia in the contralateral extremities developed in three patients in this personal series of over 50 cases. Slight weakness for from 10 to 14 days after operation was seen in four others. The remaining patients suffered no loss of motor power, a fact well documented by the motion pictures accompanying this presentation. Cases in which relief of tremor and rigidity was reported as satisfactory have been benefited without sacrifice of motor power. On the contrary, useful motor power has been increased after operation in many cases.

Handwriting: The remarkable improvement in handwriting noted in several patients, undoubtedly a reflection of the relief of tremor and rigidity, is objective evidence of postoperative improvement in functional activity.

General Disability: Perhaps the most remarkable improvement noted in certain cases has been in the area of daily life activities. Many of the cases selected for anterior choroidal artery occlusion manifested an extreme degree of helplessness. The relief of rigidity in a number of patients who had been bedridden for many years was accompanied by a rapid resumption of the activities necessary to daily living. Some patients actually returned to gainful employment after years of incapacitation. (These cases have

been followed meticulously and documented fully. Such documentation is available to students of this operation.)

Deformity: Deformities of the hand, a common disabling feature of parkinsonism, vary from the typical rigid, cupped hand to the hand flexed chiefly at the wrist and metacarpophalangeal joints, with hyperextension at the interphalangeal joints. The reversal of such deformities in several cases has been noted in this series. In some instances the deformity was of many years' standing and seemed irreversible on passive manipulation. The complete reversibility of such deformities following surgery was one of the many unexpected results observed during this investigation.

Speech: A few patients have shown considerable improvement in the ability to speak audibly and intelligibly. However, in the majority of cases with advanced weakness of the spoken voice there was no improvement. Only two of the patients who were totally unable to communicate verbally prior to operation have developed useful phonation postoperatively.

Painful Cramps: Patients who suffered painful cramps in their rigid extremities have been relieved of the pain along with the rigidity. In some instances the patient has remarked that relief of pain was the most gratifying result of the operation.

Masked Facies: Considerable improvement of masked facies has resulted in many cases. Lessening of the masked facies was obviously due, in some instances, to relief of rigidity in the facial musculature contralateral to operation.

Oculogyric Crisis: In three cases there has been a very marked lessening in the frequency and severity of oculogyric crisis following surgery. In one case the crisis has been completely absent for over two years since surgery, although it occurred almost daily and was incapacitating preoperatively.

COMPLICATIONS

The operative mortality in this series was 10%. There were three cases of hemiplegia, in one instance accompanied by a moderate degree of aphasia. There was one case of quadrantic hemianopsia. There have been five instances of oculomotor nerve palsy, all of which cleared spontaneously.

Several patients were somnolent and febrile after operation. It was found that prolonged somnolence and morbidity were more likely to occur in patients who were extremely debilitated, lethargic, perspiring, and drooling severely before operation. As mentioned earlier, vigilant postoperative care is essential to the management of these complications. Several patients were disoriented during the immediate postoperative period. Two patients experienced visual hallucinations during the first postoperative week, and two patients demonstrated choreiform movements during the same period. Several patients suffered some degree of memory defect for

several weeks following operation. In some instances the memory deficit has been longer lasting.

All complications have lessened considerably during the latter half of this series of cases. There has been only one death in the last 25 cases of anterior choroidal artery occlusion. The other undesirable side-effects have been proportionately decreased as experience has been gained. In this regard, adherence to the details of postoperative care mentioned above will help to prevent undesirable postoperative sequelae.

RESULTS OF CHEMOPALLIDECTOMY IN PARKINSONISM

The operation of chemopallidectomy has now been performed 145 times. In 125 of these instances it was performed in cases of parkinsonism. There has been marked lasting alleviation of contralateral tremor and rigidity in 70% of these 125 operations. Although in many instances complete abolition of tremor as well as rigidity has been obtained, rigidity has been more consistently and completely alleviated than has tremor. However, with increasing experience and improvement of the technic during the course of this investigation, the frequency of relief of both tremor and rigidity has been increased.

Complications in 145 chemopallidectomies are as follows: The mortality rate for chemopallidectomy at the present time is slightly less than 3%. There have been four cases of hemiparesis resulting from operation. There has been one instance of aphasia and one of ataxia and oculomotor nerve palsy.

RESULTS OF CHEMOPALLIDECTOMY IN OTHER HYPERKINETIC DISEASES

During the last 18 months, 20 chemopallidectomies have been carried out in other far-advanced hyperkinetic disorders. The diagnoses in these cases were chorea, chorea-athetosis, athetosis, or dystonia musculorum deformans. These 20 operations were performed in 12 patients, four having had a unilateral chemopallidectomy and eight a bilateral chemopallidectomy. In one instance the bilateral operations were performed at the same time. In all other instances the bilateral operations were performed in separate stages, at least one month apart. The 12 cases were categorized as follows: two cases of chorea, two of chorea-athetosis, four of athetosis or tension athetosis, and four of dystonia musculorum deformans.

Of the 12 cases operated upon, eight obtained alleviation of the involuntary movement or hyperkinetic manifestation contralateral to the side of operation without sacrifice of motor power. In two other cases, alleviation was obtained but the relief did not persist. There was one case complicated by hemiparesis, and one postoperative death. Thus, in the 12 cases there have been eight good results which have persisted, two good results which proved to be transient, one complication of hemiparesis, and one fatality.

The results obtained thus far would seem to support the hypothesis that the globus pallidus contributes actively to the mechanisms underlying various hyperkinetic manifestations. Moreover, these results would indicate that not only parkinsonian tremor and rigidity but also choreiform movements, athetosis and dystonia may be relieved neurosurgically without necessarily sacrificing motor power.

PRESENT STATUS OF CHEMOPALLIDECTOMY

Chemopallidectomy, with use of the landmarks which have now been developed and the pallidectomy guide, is a technic potentially capable of wide application in neurosurgery of parkinsonism, as well as therapy in other hyperkinetic diseases. It is a simple technic which can be perfected and utilized by many neurosurgeons. It affords an opportunity, by procaine injection, to predict the probable result of operation in a given case. It obviates the necessity of producing an identical lesion in each case, and permits one to seek out the most profitable operative site in each individual.

This operation may be used in elderly individuals who have senile or arteriosclerotic parkinsonism, as well as in the younger age groups. However, elderly patients must be selected with painstaking care, for they must be able to withstand this procedure under local anesthesia. Elderly patients with widespread senile nervous system deterioration and advanced muscular weakness or mental changes should not be selected for operation.

Although the operation of chemopallidectomy appears to be a relatively simple one, the syndrome of parkinsonism and its many neurologic and psychologic components is not. The operation should be used only by those with a detailed knowledge of intracerebral anatomy, and only for patients who have been minutely investigated and carefully selected.

SUMMARY

It has been the purpose of the foregoing report to summarize the pertinent, known, useful information regarding the neurosurgical treatment of parkinsonism. Surgeons have applied themselves to the development of surgical therapy for this malady because, up to the present time, medical therapy has not produced a lasting effect on the tremor, rigidity, deformities, incapacitation and relentless progress of the disease. Sustained interest in surgical approaches to this problem has been evidenced only during the last two decades.

Most of the earlier efforts in surgical therapy were devoted to attempts to relieve parkinsonian tremor by surgery of the pyramidal tract. The neurosurgical treatment of parkinsonism can be said to have passed through a "pyramidal tract era," starting with the cortical resections of Bucy and Klemme in 1937. Their investigations were followed by section of the pyramidal tract at the level of the cervical spinal cord and cerebral peduncle. These operations, whether at the cortical, peduncular or cord level, are

capable of relieving tremor of the contralateral extremities only to a degree proportional to the sacrifice of motor power in those extremities. Rigidity and disability have been either unaffected or worsened by pyramidal tract operations. In view of subsequent developments, there is rarely, if ever, any indication for sacrifice of the pyramidal pathway in the neurosurgical therapy of parkinsonism.

Surgery of the basal ganglia appears to be the most fruitful approach to this problem at the present time. This avenue of investigation was initiated by the surgical technics of Meyers. He developed a series of transcortical, transventricular operations aimed at removal of the head of the caudate nucleus, anterior limb of the internal capsule and pallidofugal pathways, respectively, or a combination of these structures. The clinical and physiologic significance of Meyers' contributions is noteworthy. However, the hazard of the transventricular operation, the variability of results, and the limitation in type of patients who may be selected for such procedure preclude, in Meyers' opinion, the general employment of these technics.

Spiegel and Wycis have introduced the employment of stereotactic instruments into the realm of basal ganglia surgery in humans. There can be little doubt that the development of stereotactic technics will become meritorious and significant in future approaches of surgery of the basal ganglia and other subcortical structures. Narabayashi has injected procaine in oil into the globus pallidus with his own stereotactic instrument, but has been successful only in alleviating rigidity, tremor having recurred in his cases. Several neurosurgeons have now developed their own type of stereotactic apparatus. For the most part these apparatuses are complicated, and their use has been limited to research projects in medical teaching centers. No large series of well documented follow-up results has yet been presented. Therefore, since all academic considerations must yield to the final criterion of factual results, one must await the reports of more extensive experience with the complicated stereotactic procedure in parkinsonism in order to compare its efficacy with methods which appear to be simpler and possibly more suitable to widespread application.

The two technics which have been developed and used in our personal experience with the surgery of parkinsonism have been described in detail. The operation of anterior choroidal artery occlusion is best suited for young postencephalitic parkinsonians of long duration and great incapacitation. It is an operation which has been tested in a personal series of more than 50 cases, with follow-up studies of up to three years. Its possible salutary effects have been corroborated independently by more than 25 neurosurgeons. It has the singular disadvantage of being dependent upon the vagaries of the anterior choroidal artery in any given case. This is an important factor, over which the surgeon has no control. However, it has the possibility of producing great benefit in a reasonable percentage of patients. Therefore, in selected instances, patients are justified in accepting the risks of this procedure in an attempt to harvest the possible benefits which may accrue.

The operation of chemopallidectomy is considered to have potentialities of wide and useful employment in all types of parkinsonism. The technic has the advantage of being accurate, straightforward and simple to execute. As a matter of fact, its simplicity could easily lead to abuse and incorrect usage. Such a miscarriage must be guarded against vigilantly.

In addition to the simplicity of instrumentation and technic of chemopallidectomy, this operation provides an opportunity to select the correct subcortical site for destruction in a given case by performance of an intracerebral procaine injection prior to the infliction of a permanent destructive lesion. Thus, the effect of a particular lesion in a given patient can be predicted with a reasonable degree of accuracy. The risk of this operation is low, the mortality rate being less than 3%. The possibilities of lasting benefit are good—at least 70% at the present time.

There is at present no cure for parkinsonism. There is, however, the possibility of useful alleviation of many of its symptoms by neurosurgery. This aspect of therapy in parkinsonism should therefore be considered as part of the regular armamentarium of treatment in this disease. The advisability of employing neurosurgery should be objectively considered and its advantages and disadvantages for a given case weighed carefully when that case has reached a moderately advanced state.

The accumulation of a few concrete facts regarding the pathologic physiology of tremor and rigidity has, above all, served to illustrate how little is known about this disease in comparison with what remains to be learned.

Conclusions

Surgical technics are available which, if meticulously executed in the proper cases, can produce good results in 70% of parkinsonian patients chosen for operation. Statistically, therefore, there is as much, if not more, justification for neurosurgical treatment of parkinsonism as there is for neurosurgical treatment of intractable pain, focal epilepsy, and other diseases which merit the serious attention of neurosurgeons. The approaches described in the preceding pages are new. Much remains to be learned. Undoubtedly, improvements will be forthcoming.

All in all, there appears to be reason for judicious optimism regarding the future care of patients with this tedious, distressing malady. Cautious, expert utilization of the technics described can now aid in the treatment of such patients, as well as in the accumulation of knowledge needed to advance the therapy of hyperkinetic disease.

SUMMARIO IN INTERLINGUA

Iste reporto summarisa le stato presente de duo recentemente disveloppate technicas neurochirurgic original pro le tractamento de parkinsonismo e altere disordines extrapyramidal. Iste technicas es (1) le occlusion chirurgic del arteria antero-choroidal e (2) chimopallidectomia. Ambes visa al destruction del portion

mesial del globo pallide: le prime per effectuar un infarcimento de ille structura in consequentia de un obstruction de su provision sanguinee, le secunde per destruer lo directemente per le injection de agentes neurolytic. Le datos summarisate in iste reporto demonstra que technicas neurochirurgic pote alleviar tremor parkinsonian, rigiditate, deformitate, e invalidation sin sacrificio del functiones motori o sensori del extremitates.

Occlusion chirurgic del arteria antero-choroidal,—Le objectivo de iste technica original es producer un infarcimento del portion mesial del globo pallide e de certes de su connexiones efferente. Iste manovra ha essite executate in un serie personal de 55 casos. Excellente resultatos—i.e. alleviamento de rigiditate e tremor contralateral—esseva obtenite in 70% del casos. Le mortalitate esseva 10%. Hemiplegia occurreva in tres casos. In multe casos le operation alleviava non solmente tremor e rigiditate sed etiam facie mascate, deformitate, festination, e invalidation. Le technica ha le distincte disavantage que illo depende del capricios del arteria antero-choroidal in omne caso individual. Tamen, illo offere le possibilitate de effectuar grande beneficios in un satis alte procentage de patientes. Le operation del occlusion del arteria antero-choroidal es melio appropriate pro juvene patientes de parkinsonismo postencephalitic de longe duration e grande invaliditate.

Chimopallidectomia.-Iste secunde technica original ha essite empleate 135 vices in le series hic reportate. Illo require le introduction de un cannula via un parve perforation cranial a in le globo pallide. Un guida-agulia pallidectomic de simple manipulation ha essite disveloppate pro iste objectivo. Le operation provide le opportunitate de seliger le correcte sito subcortical pro le intervention chirurgic per medio de un injection intracerebral de procaina que proba le effecto probabile super tremor e rigiditate ante le infliction de un permanente lesion destructive. Le risco de iste lesion es basse. Le mortalitate esseva 3%. Le prospectos de beneficios durative es bon. Al tempore presente illos amonta a 70%. Le operation ha le avantage additional que illo es usabile in individuos de etates plus avantiate e non solmente in le gruppo de patientes plus juvene. Recentemente, iste technica ha etiam essite empleate in selecte casos de chorea, athetosis, e dystonia. Le resultatos esseva excellente. Il ha essite demonstrate que utile grados de alleviamento de multe symptomas de parkinsonismo pote esser attingite in casos seligite per medio de intervention neurochirurgic. Quando on considera le uso de mesuras chirurgic in un caso individual, on debe evalutar le grado del invaliditate, le duration del morbo, le responsa a medication, le prognose del morbo, e le situation vital del patiente. Es discutite le indicationes e contraindicationes pro le intervention neurochirurgic in casos seligite de parkinsonismo. Le intervention neurochirurgic es etiam promittente como tractamento de certe casos de chorea, athetosis, e dystonia.

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SILAGE GAS POISONING: NITROGEN DIOXIDE PNEUMONIA, A NEW DISEASE IN AGRI-CULTURAL WORKERS*

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Two cases of acute respiratory disease due to inhalation of silage gas were encountered in August, 1954. One was fatal. A thorough investigation of these two cases and of the silage gas that caused the illness indicates that the disease was caused by the oxides of nitrogen.

A careful review of the literature indicates that, although chemical pneumonia and fatalities due to fumes of the oxides of nitrogen have been described many times in industry, they apparently have not been reported in cases of silage gas poisoning. The following two cases, therefore, are believed to be the first cases reported in the literature of poisoning from silage gas in which it was definitely proved that the noxious agents were the oxides of nitrogen.

CASE REPORTS

Case 1. A 66 year old white male farmer entered an unventilated silo on his farm at noon on August 27, 1954, and was rendered unconscious by a yellowish brown gas present above the silage. He was in the silo approximately five to eight minutes, after which he was rescued by his nephew (the second case), and immediately lowered to the ground, where he was given artificial respiration.

Following this, he recovered consciousness and appeared fairly well but he developed increasing dyspnea and cough and was then seen by his family physician. He was thereupon referred to the Perry County Memorial Hospital and arrived

there about nine hours following his exposure to the gas in the silo.

Physical Examination: On admission, examination of the patient revealed an aged, well developed, well nourished white male in severe respiratory distress, cyanotic and semiconscious. The temperature was 97.4° F.; pulse, 140 per minute and regular; respirations, 40 per minute; blood pressure, 104/70 mm. of Hg. The skin was pale, clammy and wet with perspiration. The external jugular veins were distended. The chest was emphysematous and the heart tones could not be heard. Auscultation of the lungs revealed loud, bubbling râles throughout all lung fields, posterior and anterior. Examination of the abdomen was negative. The remainder of the examination was unrevealing.

Past History: According to the family, there was no past history of pulmonary

or cardiac disease. No other past history was obtainable.

Laboratory Work: An electrocardiogram taken on admission was normal except for a sinus tachycardia. The hematocrit was 50%. The morning following admission the red blood count was 5,250,000; white blood count, 25,400; hemoglobin 100%; differential: nonsegmented neutrophiles, 18; segmented neutrophiles, 64; lymphocytes, 18. The hematocrit had increased to 54%.

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Treatment and Clinical Course: Oxygen was administered by nasal catheter, and the water bottle on the oxygen tank was filled with half water and half 70% alcohol as a wetting agent. The patient had been coughing up foamy white sputum, and the addition of the alcohol to the water produced temporary relief from the dyspnea. The patient was given Demerol and phenobarbital subcutaneously because of extreme restlessness. Gitaligin, 1.0 mg., was given orally on admission. Strophanthin-K, 0.68 mg., was given intravenously the evening of admission, and then half that dose was repeated one hour later. Within two hours the pulse rate had decreased to 102 and the respirations to 36.

Five hours following admission the above regimen had produced definite improvement. However, by the following morning the patient had gone into shock, was found to be without demonstrable blood pressure and was cyanotic. At this time 200 mg. of Cortef were given intravenously, and Levophed was begun intravenously in 5% glucose and water. Another 100 mg. of Cortef were administered intra-

venously five hours later.

The patient continued to become worse in spite of this therapy. The pulmonary edema became more severe, the cyanosis deepened, the respirations became more rapid, and the patient died at 5:00 p.m., August 28, 20 hours following admission and

29 hours following exposure to the silage gas.

Postmortem Examination: Autopsy was performed three hours following death. Significant findings at autopsy were limited to the lungs, which were found to be heavy and full of frothy, white fluid, and were completely consolidated in all of the lobes. Gross examination of the heart revealed no abnormality. The coronary arteries were patent and showed little evidence of arteriosclerosis. There were no signs of myocardial infarction or ventricular hypertrophy.

Microscopic Examination (Microscopic examinations were made by John R.

Roberts, M.D., of the Hagebusch Clinical Laboratories in St. Louis):

"Sections made of the heart revealed little of interest. There was some atrophy and fragmentation of its fibers. Brownish pigmentation was also present. There was a rather striking capillary engorgement, probably a final circulatory failure.

"The lungs presented a moderate amount of alveolar edema and a very obvious

bronchopneumonia. (See figures 1 and 2.)

"The preparations made of the liver showed both passive and active congestion. The former was represented by dilated central veins and pigment deposit in the adjacent liver cords. The latter was seen in the noticeably engorged sinusoids, generally.

"Sections made of the kidney revealed a moderate atherosclerosis of its larger

arteries. There was little scarring and degeneration of kidney substance.

"None of the tissues showed anything specific of gas poisoning. The immediate cause of death could well have been the bronchopneumonia with circulatory failure as contributory."

Anatomic Diagnoses: "(1) Acute bronchopneumonia and (2) probable circulatory failure."

Case 2. The nephew, a 31 year old healthy white farmer, was exposed to the same silage gas that caused the previously described fatality. He was exposed, however, for a lesser period of time—approximately two to three minutes, by his own recollection.

The patient entered the silo and, in order to rescue his uncle, descended into a thick yellow layer of gas which had accumulated above the silage. Following this, he left the silo and descended to the ground. He complained at that time that the silage gas was acrid and irritating to his lungs and seemed to have the odor of ammonia.

The patient was admitted for observation to the Perry County Memorial Hos-

pital about 14 hours following exposure because of weakness and vomiting. He did not appear acutely ill at the time of admission. His main complaint was that he "could not take a deep breath."

Past History: Noncontributory. There was no previous history of pulmonary or cardiac disease.

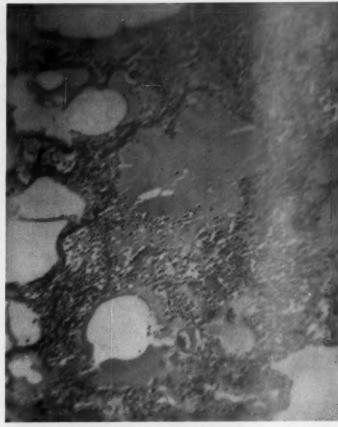


Fig. 1. Section of the lung from case 1 showing edema and areas of bronchopneumonia.

Physical Examination: Physical examination on admission revealed no positive physical findings. The heart and lungs were normal to auscultation and percussion. The blood pressure was 120/80 mm. of Hg; respirations, 18; pulse, 92 and regular.

Clinical Course: Seven hours following admission, reëxamination revealed his respirations to be shallow and rapid. There were a few inspiratory râles over the anterior portions of the chest bilaterally. The patient felt well, was alert and cooperative, and asked to be released to go home.

A chest x-ray taken at this time, however (figure 3), revealed diffuse, patchy and confluent infiltrations throughout the middle two thirds of both lung fields. The

apices and the costophrenic angles were clear. The diaphragms were normal. The cardiac shadow and bony structures were normal. The opinion of the radiologist was that this picture represented a chemical pneumonitis, apparently as a result of the inhalation of the toxic gas.

Laboratory Work: Twenty-four hours following the patient's exposure to the silage gas, the red blood count was 4,600,000; white blood count, 12,800; hemoglobin,



Fig. 2. Section of the lung from case 1 showing edema and bronchopneumonia.

97%; differential: nonsegmented neutrophiles, 10; segmented, 70; lymphocytes, 20. The urinalysis was normal.

Treatment: The patient was given intramuscular penicillin and streptomycin and nasal oxygen. He was transferred to Barnes Hospital, St. Louis, where he was attended by Donald H. Finger, M.D.

Dr. Finger's report on the clinical course of this patient after he reached Barnes Hospital is as follows: "On admission, the respiratory rate was 60, blood pressure 130/80, pulse rate 130 and the temperature 98.6° F.

"On physical examination, his general appearance was that of an acutely ill man. His skin was slightly cyanotic, as were the nail beds. Examination of the eyes revealed only minimal conjunctivitis. Examination of the chest revealed that it was held in full inspiration and the respiratory excursions were limited in depth but were extremely rapid. The percussion note was hyper-resonant. Breath sounds were



Fig. 3. Roentgenogram of the chest of case 2, showing bilateral diffuse, patchy and confluent infiltrations throughout the middle two-thirds of the lung fields.

extremely distant. There were scattered râles throughout the lungs. The heart was not enlarged to percussion. Sinus tachycardia was present. No murmurs were noted. The remainder of the examination was within normal limits. Chest x-rays taken revealed diffuse pneumonitis involving all lobes of the lungs. An electrocardiogram revealed only a sinus tachycardia. The urinalysis was negative. The blood counts were within normal limits. Electrolyte studies were basically within normal limits.

"His course in the hospital was relatively uneventful in that he responded rather dramatically to oxygen, bronchodilators and antibiotics in the form of large doses of penicillin and streptomycin. He remained afebrile and in 48 hours was clinically much improved other than for persistent râles. On the fifth hospital day, he developed a fever and the antibiotic therapy was changed to Achromycin. He became afebrile within 24 hours and remained so. Progressive chest films were taken and showed rapid clearing of the pneumonitis."

Follow-up Examination: The patient was last examined on May 11, 1955, and at that time had no complaints. There was no cough or sputum. Examination of the chest revealed a resonant percussion note. Breath sounds were within normal limits and there were no râles. The heart was negative. X-ray of the chest showed no infiltration in either lung. The trachea was in the midline. The diaphragm was

of normal contour. The heart was of normal size.

SPECIAL TOXICOLOGIC STUDIES

Special studies on these two cases were performed by officials at the University of Missouri, and the results of these studies were made available to the author by J. H. Longwell, of the Division of Agricultural Sciences, College of Agriculture, University of Missouri.¹

Gas was collected from the silo in which the two individuals had been poisoned. Chemical analysis of the actual gas, performed at the University of Missouri, indicated that this gas contained the oxides of nitrogen.²

Also, some of the corn from the same silo was brought to the laboratory and placed in a miniature silo for fermentation. The gas produced in this experimental silo was collected and chemically analyzed. This also showed large amounts of the mixed oxides of nitrogen.⁸

It was proved that the gas which came from the corn ensilage was toxic. First of all, it was noticed that around the silo in which the individuals had been stricken a great number and variety of insects had been killed. In addition, the vegetation was killed below the silo drain where the heavy gas would flow.

Albino rats were placed in a miniature silo in the University laboratory and observed under conditions similar to the silage fermentation on the farm where the accident occurred. All the rats allowed to stay in the miniature silo died.

Pfander and Muhrer * stated that several cases of forage poisoning in cattle were reported following the feeding of forage grown in 1953, when there was a severe drought in Missouri. The incidence increased in 1954 until it reached a near-epidemic proportion in central Missouri. Dozens of herds were affected, and hundreds of cattle were killed. The University of Missouri performed many tests on the forages consumed by these animals and, in most cases, the feed contained excessive amounts of nitrates. Ensiled corn plants, when high in nitrate, underwent abnormal reactions, and a poisonous yellow gas was often formed. The analysis of this gas showed that it was a mixture of oxides of nitrogen and was highly toxic to animal life.

NITRATES IN CORN ENSILAGE

A series of questions concerning corn and nitrates was put to Dr. Longwell. These questions and résumés of his answers follow:

Q. How do nitrates get into corn stalks?

A. The presence of a low concentration of nitrates in the growing plants such as corn is a normal finding. However, when temperature and moisture conditions interfere with the normal metabolism of nitrates into amino and protein nitrogen, then there is an accumulation of toxic amounts of nitrates in the corn plant. Some of the factors which increase the amount of nitrates to be found in plants are as follows:

(1) High nitrate soils.

(2) Drought, particularly if it occurs when the plants are relatively immature, may leave the vegetation high in nitrates.

(3) Ultra-violet radiation and increasing light intensities or length of photoperiod favor the assimilation of nitrates by plants.

Q. How are nitrates changed into toxic gases in the silo?

A. Potassium nitrate by anaerobic fermentation is changed into potassium nitrite and oxygen. These nitrites combine with organic acids in the ensilage to form nitrous acid, HNO₂. As the temperature of the ensilage rises with fermentation, the nitrous acid decomposes into water and a mixture of nitrogen oxides which include nitrogen trioxide (N₂O₃), nitric oxide (NO), nitrogen dioxide (NO₂), and nitrogen tetroxide (N₂O₄). The nitrogen trioxide is a brown gas, the nitrogen dioxide is a red gas, and the nitrogen tetroxide is a yellow gas. Nitric oxide is colorless.

O. What are the physical and chemical properties of the gas?

A. Nitric oxide is a very stable gas and is only slightly soluble in water. It is a reducing agent. Nitrogen dioxide readily polymerizes, is water soluble, and has an offensive odor. Nitrogen trioxide dissociates very rapidly into NO and NO₂. Nitrogen tetroxide decomposes to NO₂, is water soluble, and is an oxidizing agent.

Q. How can nitrogen oxide poisoning be prevented in human beings?

A. The prevention of this disease can be attained by education of those individuals that may come in contact with oxides of nitrogen. Rural or industrial people who work around silos or manufacturing plants where this gas may be released should be informed as to its properties and dangers. These people should know that the gas can be trapped in silos, in silo chutes or in buildings at the base of the silo. They should know that the gas is colored from brown through red to yellow and that when inhaled it produces a choking sensation. Rural and industrial safety programs should include information of possible location, detection, and physiological action of this gas.

PREVIOUS CASES OF SILAGE GAS POISONING

The literature has been searched as thoroughly as possible and the following are the cases of silage gas poisoning in humans and animals which have been discovered:

Price et al. in 1937 reported three deaths which had occurred on a farm when a mother and two daughters were overcome by gas above corn ensilage. Analysis of a sample of the gas taken at the surface of the ensilage the day following the accident revealed oxygen, 18.4%, carbon dioxide, 10.2%, and nitrogen, 71.4%. No tests were made for nitrogen dioxide and no mention was made of a brownish color of the gas. The authors felt that the deaths were due to excessive carbon dioxide.⁶

The above authors also reported the following earlier and similar cases:

1. A North Dakota farmer was overcome while attempting to clean the pit of his silo. Four of his children also were suffocated in trying to rescue him. All five died. One other man was overcome but was rescued.

2. Two farmers in Ohio were suffocated when they entered a partially filled silo in the morning to resume the work of filling the silo and tramping the ensilage commenced the day before. The official opinion was that carbon dioxide was the toxic agent.

3. Two men were asphyxiated in a steel bin at a grain company plant in Chicago as the result of entering a bin filled with damp corn.

4. A workman was asphyxiated at a grain-handling plant in Utah when he entered a concrete bin filled to within seven feet of the top with damp barley. Analysis of the air above the barley showed oxygen, 3.48%, carbon dioxide, 12.65%, and nitrogen, 83.87%.

5. Two employees of a grain elevator company in Illinois were asphyxiated in a 12' by 12' tile bin about half full of damp oats. Both men died.

A report was discovered about eight chickens and many insects that were killed by yellow gas coming out of a silo in 1949. This report also included that of a man overcome by the same gas. The man was quickly rescued and recovered.⁷

Fostvedt in 1951 reported a case of a 25 year old man who had entered a previously closed silo and became unconscious shortly after entering the silo. He was unconscious for one hour after being retrieved from the silo. The author incriminated carbon dioxide as the toxic gas in this case.⁸

Two heifers were reported in 1952 to have been killed by nitrogen dioxide gas which had come down a silo chute.9

The author of a question in the "Queries and Minor Notes Department" of the October, 1953, issue of the Journal of the American Medical Association ¹⁰ reported the death of a 19 year old man found in a silo that had been filled with new silage 24 hours before. In the answer to the question the consultant said that the toxic gas was carbon dioxide. He did not men-

tion the oxides of nitrogen. He also stated that the absence of oxygen may have accounted for this death.

Poisoning by Oxides of Nitrogen in Industry

The effects of nitrous and nitric gases on 23 men were reported in 1945 by Charleroy. Nine men were seriously affected. The gases were caused by a fire adjacent to a supply of blasting gelatin used for boosters in hand depth charges. The blasting gelatin caught fire and gave off thick, yellowish green fumes. Two of the nine men showed signs of circulatory collapse 15 to 16 hours after exposure to the gas. These two men died. It was noted that there were no symptoms immediately after exposure. The symptoms developed from four to 24 hours later, and all of the cases presented similar prodromal symptoms. The suddenness of the appearance of serious symptoms and complications was a striking feature.

The prodromal symptoms were headache, a sensation of fullness in the head, a sense of tightness in the chest, and a slight cough. The 14 who were least affected by the gas presented no other symptoms.

McAdams and Krop ¹² recently reported two cases of serious pulmonary disease due to the fumes of nitric acid. These cases were caused by the fumes of red fuming nitric acid which contains dissolved oxides of nitrogen. These authors state that there are four distinct clinical pictures of acute poisoning by inhalation of nitrous fumes, as have been described by Flury: ¹³

1. The *irritant gas* type, in which there is local irritation followed by a latent period of a few hours and then the development of pulmonary edema, with death in one to two days.

2. The reversible type, in which there is a rapid succession of dyspnea, cyanosis, vomiting, vertigo and sometimes unconsciousness.

3. The *shock* type, in which there is a very rapid onset of signs of suffocation, convulsions and cessation of breathing.

4. A *combined* form, in which there are early cerebral symptoms that subside after removal from the fumes, but after a period of a few hours pulmonary edema develops.

Adley 14 reported acute oxides-of-nitrogen poisoning in a shrinker, followed by death 10 days later from chemical pneumonia.

Rossano ¹⁵ reported a case of a man who died 26 hours after exposure to the fumes of nitric acid. The autopsy showed pulmonary edema, acute tracheobronchitis and bronchopneumonia. Feil ¹⁶ reported four cases of men exposed to the fumes of nitric acid when a large bottle containing 40 L. of nitric acid was broken and the acid spilled on the ground. The symptoms were characterized by oppression in the chest, respiratory difficulty, pallor, cyanosis and syncope. Three of these patients developed symptoms as above but recovered after a short period of time and returned to work. The author warned that, even though the patient may complain only of a little

throat irritation and cough after exposure to the fumes and may continue working for many hours, he may still develop severe intoxication after a period of several hours. He suggested that the best way to avoid serious sequelae is to have the patient rest not less than 24 hours and to have stimulants. If pulmonary edema ensues, the author suggested oxygen and cardiac stimulants as treatment.

McConnell ¹⁷ warned against the exposure to concentrations of nitrous fumes in the manufacture of high explosives and smokeless powder. He wrote: "Following a serious exposure, there may be a latent period of 5 to 24 hours during which the employee may feel well and go about his business or leave the plant at the end of a shift. Some hours later, there may develop a sudden onset of congestion in the lungs which may rapidly lead to shock and death if not vigorously treated." The author stated that exposure to oxides of nitrogen has, in the past, been confined almost entirely to three industries: the smokeless-powder works, the TNT and explosive works, and the chemical works.

SILOS AND TOXIC ENSILAGE

Fabian ¹⁸ stated that every year casualties are reported and that sometimes death results from asphyxiation of workers by carbon dioxide gas arising from fermentation in silos. Numerous studies on ensilage have shown that the green fodder, on being placed in the silo, immediately begins to undergo changes opposite to normal plant metabolism. The oxygen of the surrounding air is consumed and carbon dioxide gas liberated. Because of the high specific gravity of carbon dioxide, it tends to remain at the surface of the ensilage and for a few feet above. Records show that most of the silo accidents occur in the morning, apparently after fermentation has taken place during the night or over Sunday.

The Farmers' Bulletin on silos 19 contains a warning concerning the gas danger in silos: "Suffocating gas from fermenting silage, mostly carbon dioxide, forms in all silos shortly after filling begins and continues until the fermentation stops. . . . Many lives have been lost because of carelessness in entering the silo where there may be danger of gas. . . . A victim of silo gas suffers from lack of oxygen and should be moved into fresh air as soon as possible and artificial respiration applied." It is to be noted that this was published in 1948 and that at no point in this publication is the danger from oxides of nitrogen mentioned.

Hogan ²⁰ reported numerous instances in which a brown gas has been noticed above ensilage. The amount of nitrate that is toxic in the ensilage when eaten by cattle is 0.41% of potassium nitrate. Some samples of corn stalks during drought conditions have been found to contain as much as 6.7% of potassium nitrate. There is much more nitrate in the stalk than in the leaves of the corn plant. It has also been definitely shown that when there is a large amount of nitrate in the soil there is a much larger ac-

cumulation of potassium nitrate in the plant. It is emphasized that a severe drought has a marked effect on the accumulation of nitrates in immature plants.

The Agricultural Gazette of July, 1939, 21 contained instructions on how to prevent deadly gases from accumulating in silos. It was suggested that the crop should have reached the proper stage of maturity and should not be too dry. Carbon dioxide is incriminated, and oxides of nitrogen are not mentioned. It was stated that, in exceptional cases, the gases given off may be inflammable. Therefore, a candle should not be lowered in a silo to test for carbon dioxide—a guinea pig or a fowl should be used instead.

A consultant to the Queries and Minor Notes Department of the *Journal* of the American Medical Association in 1932 ²² stated that the prime harmful gas associated with the storage of ensilage is carbon dioxide, and that this gas may exist in quantities of up to 75%. The author stated further that there may also be irritants in the gas composed of volatile ingredients such as butyric, propionic and lactic acids. Oxides of nitrogen are not mentioned.

TOXICOLOGY OF OXIDES OF NITROGEN

The common oxides of nitrogen 28 are nitrous oxide (N_2O) , nitric oxide (NO), and two forms of a dioxide $(NO_2$ and $N_2O_4)$; in addition, there are the trioxide (N_2O_3) and the pentoxide (N_2O_5) . At ordinary temperatures the trioxide and pentoxide decompose and, on contact with air, react in such a way that the principal product is a mixture of NO_2 and N_2O_4 .

Nitrous oxide has no irritating action and is used extensively as an anesthetic for surgical operations and dental extractions. Nitric oxide (NO) at ordinary temperatures reacts with oxygen or air to form brown nitrogen dioxide (NO₂).

Nitrogen dioxide (NO₂) and its dimer, nitrogen tetroxide (N₂O₄), are the oxides responsible for the toxicity. At room temperature this is an orange gas, which becomes reddish brown as the temperature rises. This gas is responsible for the yellowish brown color usually associated with the oxides of nitrogen in the air. When nitrogen dioxide is inhaled it is at once changed to that molecular form corresponding to the body temperature. At 40° C., therefore, approximately 30% of the dioxide is in the form of NO₂ and 70% in the form of N₂O₄. N₂O₄ reacts with water in the respiratory tract to produce nitric and nitrous acids. The NO₂ reacts with water and oxygen from the air to produce nitric acid and nitric oxide. These acids react with the alkali salts in the tissues of the respiratory tract forming nitrates and nitrites, and in so doing have an irritative action. The nitrates have no effect, but the nitrites when absorbed exert a systemic action. This phenomenon, however, does not play an important part in poisoning.

Because of the insidious action of the gases of nitrogen oxide, it is necessary that anyone who has inhaled a considerable amount of this gas be

removed at once to a hospital for immediate treatment. After a latent interval the patient develops pulmonary edema. Following this the patient may develop pneumonia, bronchiectasis or emphysema. Methemoglobinemia may also occur.

The permissible concentration of oxides of nitrogen in the atmosphere at work places has been set at 25 parts per million for eight hours per day.

DISCUSSION

It is apparent from the foregoing review that silage gas poisoning due to the oxides of nitrogen is a little-known disease and one that has not been adequately reported in the medical literature.

Under ordinary circumstances, when there is sufficient moisture for the production of normal corn plants, high concentrations of nitrates do not occur in the corn stalks and the abnormal chemical reactions that produce oxides of nitrogen do not take place. Therefore, in normally wet years poisoning by oxides of nitrogen will not be suspected, but rather, if any silage gas poisoning cases do occur, their cause can usually be ascribed to carbon dioxide or to asphyxia from oxygen depletion.

In years of drought, however, in areas where irrigation is not common practice, it may be expected that high concentrations of poisonous nitrates will occur in corn ensilage, which will be poisonous when fed as fodder to cattle and other beasts and will produce noxious gases in unventilated silos.

The disease produced by inhaling the gases from high nitrate ensilage is in every way identical to the disease described in industrial toxicology as that produced by the fumes of nitric acid and from other sources of nitrates, such as gunpowder and other explosives. This disease is essentially an acute chemical pneumonitis which is generalized over the entire pulmonary structure. It is caused by the toxic action of nitrogen dioxide in the respiratory tree, producing a reaction which essentially is due to nitric and nitrous acids. This produces an intense inflammatory response after a latent interval of from one to many hours which then progresses to either minor or severe forms of chemical bronchopneumonia. The longer the exposure to the noxious gases, and the more intense the fumes, the more severe the pneumonia. If the exposure has been severe, there is little that present therapy can offer in preventing fatalities.

The treatment of this disease is nonspecific and primarily supportive until the organism can recover pulmonary function by natural means. Oxygen should be given. Probably oxygen under pressure during the phase of pulmonary edema would be of benefit. Antibiotics must be given to prevent secondary bacterial pneumonitis. The methemoglobinemia caused by nitrites apparently has not been a serious problem in the reported cases. However, studies should be done on this aspect of the problem; and if methemoglobinemia is found to be a significant cause of the disability, treatment should be directed toward alleviating this aspect of the disease. Broncho-

dilators are indicated but are probably of minimal value. Should evidence of cardiac decompensation occur, digitalization should be instituted.

SUMMARY

1. Two cases of silage gas poisoning are presented, one of them fatal. The oxides of nitrogen were definitely found to be the noxious agents.

2. Silage gas poisoning due to oxides of nitrogen is essentially a diffuse chemical bronchopneumonia caused by the irritating action of nitrous and nitric acids on the respiratory tree. The disease may be mild or severe, depending upon the degree of exposure. Nitrogen dioxide pneumonia has been described many times in industrial toxicology but apparently has not previously been described in the medical literature as due to inhalation of gases from ensilage.

3. Special studies done on the corn ensilage and on the actual gas from the silo in which the two patients were poisoned proved that there was a poisonous concentration of the oxides of nitrogen. This condition was due to a combination of drought, high-nitrate soils and an unventilated silo. Other studies demonstrated the toxicity of the actual gas and of experimentally-produced gas from the same ensilage.

4. The literature on silage gas poisoning is reviewed. Heretofore, all silage gas poisoning in man was thought to be due to carbon dioxide inhalation or simple asphyxia.

5. The industrial and agricultural literature on the toxicology of nitrogen oxides and on silos and toxic ensilage is reviewed.

6. Silage gas poisoning due to the oxides of nitrogen with the production of chemical pneumonia is a disease which probably occurs more commonly than is recognized. Physicians in rural areas should be aware of the possibility of this disease during summer periods when corn is being placed in silos, particularly during times of drought.

7. No specific treatment is known for the resulting bronchopneumonia. Research should be directed toward the discovery of a specific therapy.

ADDENDUM

Since this paper was submitted for publication, Lowry and Schuman at the University of Minnesota have informed the author of four additional cases. In the fall of 1955, they encountered four cases of nitrogen dioxide pneumonia among farmers giving a history of entering silos shortly after filling with dry corn, all of whom presented clinical and roentgenographic findings of bronchiolitis fibrosa obliterans. Of these, two died and at autopsy showed the condition in classic form.

The authors describe this as a newly recognized clinical entity caused by the inhalation of oxides of nitrogen produced in recently filled silos. They have chosen to designate the syndrome as "silo-filler's disease," indicating its limitation to silo workers and also its occurrence predominantly among individuals inhaling fumes from freshly filled silos. Lowry and Schuman suggest that there is a hypothetical spectrum of nitrogen dioxide poisoning in men. They suggest that there are six different degrees of exposure with correspondingly different clinical syndromes resulting from exposure to nitrogen dioxide.

In the most severely exposed (500 parts per million or more of nitrogen dioxide in air) the patients develop acute pulmonary edema with death in less than 48 hours. In patients exposed to concentrations of 300 to 400 parts per million of nitrogen dioxide, pulmonary edema with bronchopneumonia develops with death in 2 to 10 days. Those who are exposed to concentrations of 150 to 200 parts per million develop bronchiolitis fibrosa obliterans which is fatal in three to five weeks. Others who are exposed to 50 to 100 parts per million develop bronchiolitis with focal pneumonitis lasting six to eight weeks with spontaneous recovery. They suggest that individuals exposed to concentrations of nitrogen dioxide in the range of 25 to 75 parts per million develop varying degrees of bronchitis and bronchopneumonia with complete recovery. One of their most interesting hypotheses is the possibility of development of chronic pulmonary fibrosis and emphysema in individuals who have chronic intermittent exposure to concentrations of nitrogen dioxide in the order of 10 to 40 parts per million. This may explain some instances of so-called "farmer's lung."

Delaney, Schmidt and Stroebel of the Mayo Clinic have recently published an article on "Silo-Filler's Disease," ²⁵ the first article in the medical literature to be published about this disease.

The authors report two cases of severe pneumonitis in farmers who had worked inside silos with corn silage. The first patient was a 43 year old farmer who had had three episodes of pneumonia prior to his fatal episode. It was implied that the three nonfatal episodes of pneumonia might have been due to silage gas poisoning. The fatal episode of pneumonitis occurred in October, 1955, following five days of work in cleaning out old silos and filling them with new corn silage. A postmortem examination in this case revealed extensive congestion and edema of all lobes of both lungs.

The second patient was a 59 year old farmer who became acutely ill in August, 1955, after working in a silo in which there was newly chopped corn silage. The patient remembered noticing acidlike fumes in the form of a thin haze in the silo. He developed a chronic pulmonary disease which became acute about one month after he had worked in the silo, at which time he was admitted to a hospital where a roentgenogram of the thorax revealed extensive, bilateral, diffuse miliary mottling. He was treated by bed-rest alone and, three weeks following his admission, was clinically well.

The authors review experimental work done by Peterson and his coworkers at the College of Agriculture, University of Wisconsin, on the production of oxides of nitrogen by corn silage, and conclude that their two cases were caused by the inhalation of excessive amounts of nitric oxide and nitrogen dioxide.

The authors speculate about the relationship between the pneumonitis caused by nitrogen dioxide and a syndrome of pulmonary fibrosis among farmers, known as "farmer's lung." They suggest that if pulmonary fibrosis proves to be the troublesome sequel among those patients who survive, consideration should be given to the prescription of cortisone, in addition to the use of antibiotic agents and supportive therapy, as a possible means of retarding such fibrosis.

SUMMARIO IN INTERLINGUA

Es describite duo casos de acute pneumonitis causate per le inhalation de gas de bioxydo de nitrogeno in un silo. Un patiente moriva de edema pulmonar 29 horas post su exposition, le altere se restabliva.

Solmente sex altere casos de pneumonia a bioxydo de nitrogeno causate per le inhalation de gas de insilage es cognoscite. Illos occurreva in 1955. Sin dubita, il non se tracta hic de un nove morbo, sed illo es un morbo que ha solo recentemente essite recognoscite per le profession medical. Illo es probabilemente plus commun que lo que es indicate per le total de octo casos.

Sub conditiones ordinari—quando le humiditate suffice pro le production de normal plantas de mais—il non occurre alte concentrationes de nitratos in le cannas de mais, e le anormal reactiones chimic que produce oxydos de nitrogeno non ha loco. Ergo, in annos de humiditate normal, invenenamento per oxydos de nitrogeno non es a suspicer. Si nonobstante il occurre casos de invenenamento per gas de insilage, lor causa pote usualmente esser trovate in bioxydo de carbon.

Tamen, in annos de siccitate—in areas ubi irrigation non es un practica commun e ubi fertilisation per nitratos es costumari—on pote expectar le occurrentia de alte concentrationes de nitratos in mais insilate. Isto es toxic quando alimentate al bestial e altere animales e produce un gas pesante que contine grande concentrationes de oxydos de nitrogeno durante le periodo de fermentation.

Le morbo producite per le inhalation de gases ab insilatos ric in nitrato es identic in omne respectos con le morbo describite per toxicologos industrial como effecto de vapores de acido nitric e de vapores ab altere fontes de nitrato, como per exemplo pulvere de cannon. Le morbo pote esser designate accuratemente como "pneumonia a bioxydo de nitrogeno." Illo es un acute pneumonitis chimic que es generalisate in le integre structura pulmonar. Bioxydo de nitrogeno es inhalate e alterate in acidos nitric e nitrose, e istos—post un intervallo latente de inter un e multe horas—produce un intense responsa inflammatori. Isto causa minor o sever formas de broncho-pneumonia chimic. Quanto plus longe le exposition a bioxydo de nitrogeno e quanto plus intense le vapores, tanto plus sever es le pneumonia que resulta. Si le exposition ha essite sever, il ha pauco in nostre currente cognoscentias therapeutic a prevenir un exito letal.

Le tractamento de pneumonia a bioxydo de nitrogeno es nonspecific e primarimente supportative usque le patiente pote restaurar su functiones pulmonar per medios natural. Le administration de oxygeno es desirabile. Oxygeno sub pression durante le phase del edema pulmonar esserea probabilemente benefic. Antibioticos debe esser administrate pro prevenir infectiones bacterial secundari. Le methemoglobinemia causate per nitratos non pare haber essite un grave problema in le casos reportate. Bronchodilatatores es indicate, sed illos es probabilemente de pauc valor. On ha

proponite le uso de cortisona. Si discompensation cardiac deveni evidente, digitalisation es necessari. Recercas deberea esser interprendite pro discoperir un therapia specific pro le morbo.

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PSEUDOMEMBRANOUS ENTEROCOLITIS AND ANTIBIOTICS *

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Introduction

Pseudomembranous inflammation of the intestine has been recognized for over a century. During the last several years there has been an apparent increase in its incidence. Disagreement has existed regarding the role of antibiotics in the etiology of this condition. Some authors claim relatively no increase as the result of widespread use of antibiotics, whereas others take the opposite view. Recent experiences, however, which indicate the etiologic importance of antibiotic-resistant staphylococci have produced a greater alertness and suspicion by physicians generally, and more antemortem diagnoses are being made. The precise role of the antibiotics has not been definitely established, but evidence exists that their use creates a situation, at least with reference to the staphylococcus, which favors the occurrence of a pseudomembranous inflammation in the intestinal tract. This dangerous reaction, resulting frequently from the injudicious use of antibiotics, might well be prevented or alleviated if there were a more thorough understanding of its pathogenesis and clinical characteristics.

The source material is derived from the case records of several small hospitals. Case histories and autopsy findings will be presented, as well as a review of the literature concerned with this subject. The purpose of this presentation is to attempt to show that antibiotics, through their antibacterial properties, are one factor in producing pseudomembranous enterocolitis, although they are but one of many etiologic agents leading to this condition. That antibiotics are the sole cause of this condition can easily be eliminated by a study of the literature. It is difficult to prove that an increase in incidence can be ascribed to their use, yet one need but look at the huge amounts of antibiotics being administered, as well as note the verbal reports of colleagues in this area, to become impressed with the seriousness of the situation.

ETIOLOGY, PATHOLOGY AND PATHOGENESIS

The concept of pseudomembranous inflammation is not new. Several medical textbooks edited between 1849 and 1880 54, 55, 56, 57 described an acute inflammatory reaction of the mucous membranes, particularly of the intestine, due to the action of poisons or other irritants. Joseph Coats, 1 a Glasgow pathologist, in his text edited in 1883, described the reaction in the intestinal

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lining as resulting from "specific morbid poisons" producing a violent irritant action leading to a "catarrhal inflammation," and finally to a "phlegmonous" reaction with sloughing of the mucous membrane. The "mucous membrane becomes swollen by serous exudation, is soft and juicy and thrown into folds, on the summits of which it is peculiarly hyperemic, with the surface being covered by mucous or grumous material consisting of shed epithelium with mucous and inflammatory exudation. The mucous membrane and submucous tissue are infiltrated with serous fluid and leukocytes in great abundance." In more advanced stages more thickening, hemorrhage and necrosis were noted, "... and if slough surrounds the gut we may have a ring of necrosed tissue ultimately discharged from the anus." He felt uncertain as to whether the poison acted on the surface of the mucous membrane because it was present in the intestinal contents or because it was carried in the blood.

In another text, published in 1898, Lazarus-Barlow 2 described the reaction as being characterized by an inflammatory exudate of a "highly albuminous character, autocoagulable, probably due to the leukocytes present." When such an exudate went on to coagulate it was called a serofibrous or fibrinous exudate, which was likely to yield a membrane. The classic membrane of diphtheria caused by the powerful necrotizing diphtheria toxin is such an exudative membrane, being considered interstitial in character and difficult to remove. Hence, the term "diphtheritic" has been applied to membranes of this type. This type of false membrane, occurring in the intestine, on the surface of wounds, in the pharynx or larynx or other surfaces, is merely a descriptive term, not solely secondary to a specific diphtheria infection.

In Reiman's translation of a text of pathology by Kaufman, at the author outlines some of the conditions which may lead to pseudomembrane formation in the gastrointestinal tract. Included are:

- "(1) The true dysenteries.
- "(2) Various infectious diseases or previously existing diseases, such as pyemia, puerperal fever, cholera, tuberculosis; more rarely small-pox, and very rarely true larvngeal diphtheria.
- "(3) Conditions of fecal stasis with the production of chemical products and mechanical pressure, as in the area of the bowel above a stenosis as in carcinoma of the intestine.
- "(4) Chemical poisonings as in uremia, 'ptomaine poisoning,' arsenic, bismuth and mercury intoxications.
- "(5) After operative procedures such as resections with the production of an artificial anus.
- "(6) Direct infection from without."

Obviously here, long before the antibiotic era, certain factors were recognized as being related to pseudomembranous inflammation. It is well to

note that, in many of the situations listed, present-day therapeutics would include antibiotics. The latter could easily be incriminated as the prime factor in producing the reaction in question. The above will also serve as testimony to the fact that surgical procedures alone are not responsible, and that medical illnesses can result in membrane formation in the intestinal tract.

An early, oft-quoted reference in the American literature is that of Finney,⁵⁰ who in 1893 reported the case of a 22 year old Negro female who underwent a gastroenterostomy for a cicatrizing ulcer of the pylorus. The patient developed a steadily increasing diarrhea and died on her fifteenth postoperative day. An autopsy performed by Simon Flexner, at The Johns

Hopkins Hospital, revealed a "diphtheritic colitis."

More recent texts of pathology 4, 5, 6 also regard pseudomembranous inflammation of the intestinal tract as a reaction to various toxic agents. True chemical poisons, such as mercury, may cause a coagulative necrosis with shallow ulcerations in the mucous membrane, as well as a diphtheritic membrane. In bichloride of mercury poisoning some evidence exists that the salt may be excreted into the lumen of the large bowel after being absorbed into the blood stream at higher levels. It offers an example of a method by which a chemical or irritant effect can be exerted through the blood stream. Arsenical poisoning can likewise produce a pseudomembrane in the large and small intestine. Several authors 3, 4, 6 present evidence that in intestinal obstruction, with retained feces, exposure of the bowel wall to pressure and bacterial action, along with dilatation and stretching of the wall, may be etiologic factors. With dilatation and stretching of the bowel wall ischemia may result. This relationship will be discussed later, as it is brought out in other reports 9, 10, 11 in which a sizeable proportion of patients underwent operation for obstructive lesions and no antibiotics were used.

Because shock was consistently present in the autopsied cases of Penner and Bernheim,⁷ it was postulated that shock itself was the prime etiologic factor. These authors reviewed the literature up to 1931, quoting the experiences of various European investigators. Penner and Druckerman ⁸ later reported nine cases of postoperative diphtheritic enterocolitis, correlating the clinical and anatomic findings, and concluding that the lesion was a nonspecific response to a wide variety of stimuli in which the common factor was shock. Their evidence tended to support the view that similar reactions in the intestine could be caused in animals experimentally by producing shock. Other authors ^{8, 11} suspect that terminal adrenal insufficiency is a factor in the production of shock, and that shock is the end result of the pathologic process produced by severe toxemia and its associated disturbed physiology. Pettet et al.¹¹ support this view.

Bacterial factors, although recognized early, are of particular interest with relation to the use of antibiotic drugs. True bacillary dysentery may result in the formation of an enteric pseudomembrane.^{3, 4, 5, 6} Streaks of

hemorrhage may occur, and evidence of death of the mucosa is frequently present, leading to ulceration and membrane formation. Sloughing may occur in smaller isolated or larger confluent areas, and scarring may be the result. After long and debilitating illnesses, streptococci or other organisms of the intestinal lumen may attack the wall of the stomach or intestine and produce a phlegmonous gastritis or enteritis, the submucosa becoming greatly thickened by the intense inflammatory reaction, thus leading to an inflammatory exudate loaded with streptococci. The invasion of any mucous membrane by bacteria or the destruction produced by a chemical irritant may lead to a necrotic, inflamed surface, cemented or welded together with fibrinous exudate into a membrane-like film.

The pathologic picture of pseudomembranous enterocolitis is well presented by Reiner, Schlesinger and Miller, 18 who studied five cases out of a series of 213 autopsies, of which 49 patients had received Aureomycin or chloramphenicol, or both. These cases involved the colon only, where yellowish gray plaques were found that varied from soft moist deposits to those which were dry and firm. Discreteness and confluency of the lesions were quite variable. The pseudomembrane seemed to vary in severity from a mild "muco-epithelial," through "fibrinopurulent," to a more severe "muco-fibrino-purulent" exudate. Stromal necrosis, "diphtheritic necrosis," the most severe reaction, was in some cases seen to blend into the viable, healthier stroma with little or no demarcation, and with varying adherence to the underlying tissue. Cellular infiltration and edema were usually present.

Penner and Bernheim describe the lesion as developing in stages, the first of which consists of submucosal vasodilatation extending into the mucosal layer. Submucosal edema follows, and focal hemorrhages are noted near the distended blood vessels. Focal areas of mucosal necrosis occur, spreading and becoming confluent and extending into the submucosa. In extreme cases the necrotic process is accompanied by an inflammatory cellular reaction. Hyaline thrombi are occasionally noted in the smaller vessels. The cases presented were those following operation and were not related to the use of antibiotics. Because of the universal presence of shock in these cases and because a similar picture is produced in experimental shock in animals, the authors contend that shock is a cardinal etiologic factor. Cases of foreign authors quoted by Penner and Bernheim involved mainly postoperative cases, the pseudomembrane reaction following such operations as those for relief of pyloric stenosis, gastric resection, gastroenterostomy, perforated duodenal ulcer, operation for ovarian cysts, and rectal and colonic surgery. Their report of the literature includes the report of Goldschmidt and Mulleder, in which in three cases a diphtheritic colitis followed operation for brain tumor, and in one case followed operation for spinal fracture. Five other cases were mentioned where the reaction occurred following spinal fracture without operation having been performed. Other cases reported by foreign authors included those following lobectomy, burns and gastrointestinal hemorrhage.

The cases mentioned above occurred in the pre-antibiotic era and were primarily postoperative. Instances following medical illnesses or directly related to infections have been well documented for many years. More recently Kleckner et al., 10 in a study at the Mayo Clinic covering the years 1940 through 1950, reported 14 cases in which pseudomembranous enterocolitis was not preceded by operation. In seven of the cases the colitis was of such severity as to be considered the immediate cause of death, whereas in the remainder the lesions were scattered and were considered only contributory. The primary cases were made up of neoplastic obstruction of the large intestine in four cases, cardiac disease in two cases, and streptococcal septicemia with bronchopneumonia in one case. It is therefore apparent

that this condition is not solely a postoperative complication.

There has been an increased incidence of the pseudomembranous intestinal involvement in patients treated with antibiotics in the past several years. At the beginning, when larger dosages of the various broadspectrum antibiotics were recommended, the physician was likely to see frequent gastrointestinal reactions, consisting of both gastric and intestinal irritation. It is likely that these were minor reactions not specifically related to the serious type considered here, but it was frequently noted that the reactions occurred most frequently when the dosage was high and when the drugs were used over prolonged periods. In the more severe reactions in which pseudomembranous processes have occurred, the broad-spectrum antibiotics were usually the offenders. It should be noted, however, that other antibiotics, either singly or in combination, have been involved. Reiner et al.18 studied seven cases which followed the use of antibiotics and presented their reasons (considered by them to be circumstantial) for believing the antibiotics to be in some way related to or responsible for the process. The colitis encountered was not epidemic, occurring under hospital supervision without a history of any antecedent illness and without demonstrable pathogens. No other drugs were used in treatment which would have been likely to produce diarrhea. The diarrhea occurred after the institution of treatment with Aureomycin, chloramphenicol, or both. All of their cases had similar sequential morphologic changes which seemed understandable.

At this point two features should be mentioned with regard to pseudomembranous enterocolitis. Diarrhea is not necessarily present in all cases.^{11, 16, 18} The absence of demonstrable pathogens may have resulted from inadequate bacteriologic technic; which, e.g., was often unsuitable until recently for the isolation of the pathogenic staphylococci.¹¹

Some authors have presented evidence that pseudomembranous enterocolitis as a complication of surgery has not increased since the introduction of the antibiotics. Pettet et al.¹¹ studied 94 postoperative cases dying as a direct result of this complication at the Mayo Clinic between 1925 and 1952. They thought that an increase noted in the years 1947, 1951 and 1952 was proportionately related to increased numbers of surgical cases in these years. Forty-five cases occurred from 1925 to 1938, 49 from 1939 to 1952. No statistics are available after 1952. The authors point out that, prior to 1948, not one case of pseudomembranous enterocolitis was diagnosed ante mortem, but that, since 1948, 26 cases have been correctly diagnosed as a result of better understanding and suspicion. Between 1938 and 1952, 40 such fatalities occurred following the use of antibiotics. The operative diagnosis in 107 cases of localized and generalized pseudomembranous enterocolitis reported by Pettet et al.¹¹ is given in table 1.

Eighteen patients received either Aureomycin or Terramycin, usually in combination with penicillin or streptomycin. Thirty-one received penicillin and 23 received streptomycin. These authors found little to support

Table 1

Operative Diagnosis in 107 Cases of Localized and Generalized
Pseudomembranous Enterocolitis

Diagnosis	Number of Cases
Carcinoma of colon	43*
Peptic ulcer	12†
Cholecystitis	11*
Carcinoma of stomach	8†
Chronic ulcerative colitis	8† 2
Benign prostatic hypertrophy	4†
Carcinoma of the bladder	3†
Appendicitis with rupture	3†
Malfunctioning of gastroenterostomy	2
Pelvic inflammatory disease	2 2*
Exophthalmic goiter	2*
Miscellaneous	15*

* Two patients in this group had localized lesions.
† One patient in this group had localized lesions.

the view of Penner and Bernheim ⁷ that shock is the primary cause, or the theory of Reiner and associates ¹⁸ that it is directly related to the use of antibiotics.

In summary, the etiology and pathogenesis of pseudomembranous enterocolitis involve a rather wide variety of responsible factors. The cause in one case may be related to inorganic or metabolic poisons, whereas in another direct bacterial infection may be the main factor. Mechanical factors may be primarily responsible in other situations. Resulting physiologic alterations appear to result in a state of shock which, if uncorrected, produces death. Antibiotics appear to play a significant part in the development of the condition in many instances. They cannot, however, be solely responsible for all cases. Multiple factors are probably responsible, even in cases in which antibiotics have been administered.

THE PROBLEM OF BACTERIAL RESISTANCE AND SUPERINFECTION

The widespread enthusiastic acceptance of new methods of treatment usually gives way to a more cautious attitude as observations of untoward side effects are made in clinical practice. Such has been the case in the use of the antibiotics. Medical research has been prompt in discovering the causes of reactions which have occurred after the introduction of the sulfonamides, penicillin and streptomycin. With the introduction of the broad-spectrum antibiotics new problems have appeared, and we are particularly interested here in the development of bacterial resistance, alteration in bacterial flora in body cavities, and superinfection. These result from the peculiar adaptive mechanisms of certain bacteria and the alteration in the homeostatic equilibrium of the normal bacterial flora of the body. Important also is the introduction or the appearance of a usually nonpathogenic bacterium in the same or some other organ, where it becomes pathogenic. This is frequently the case with the staphylococcus because of its ability to

adapt itself to potent antibacterial agents.

The development of resistance by certain bacteria to the antibiotic drugs has been described by Garrod. 15 Bacteria may react to a chemotherapeutic drug in various ways, including (1) suppression, the drug having either a lethal or an inhibitory effect: (2) habituation to the drug or the acquisition of resistance; (3) development of dependency on a drug, or (4) stimulation by the drug. Thomson 22 has attributed the resistance to such mechanisms as strain selection, adaptation and mutation. He points out that during antibiotic therapy other organisms frequently may appear which have not at any time shown sensitivity to any antibiotic, a process to which the term "superinfection" has been applied. Examples include new oral or pharyngeal pathogens found after the use of penicillin, the development of fungus infections in various areas of the body, and pseudomonas and proteus infections 40 occurring in the respiratory and urinary tracts. Rantz 21 has described superinfection as being "the appearance of an infectious process caused by an organism different from that which was responsible for the initial infection for which the patient was brought under antimicrobial therapy." The superinfection may occur in the same area or in an area different from the original process.

The competition which exists among the various bacteria in the intestinal tract or in other body cavities is in reality a protective mechanism for the host. This complex balance is frequently upset by the prolonged administration of the antibiotic drugs, particularly those of the broad-spectrum type. Smith ²⁸ has pointed out that most of the antibacterial antibiotics are the products of fungi, whereas frequently the antifungal antibiotics are the products of bacteria. The latter have a limited usefulness, however, because of their toxicity. As Smith emphasizes, "The bacteria and fungi were employing antibiotics as offensive weapons long before they were discovered

by man."

Specific instances of the effects of changes in the ecology of an organ system have been described.²¹ The development of mold and yeast infections in the oral cavity after the use of penicillin was recognized early, as distinct from the local sensitization effect. Similarly, vaginal monilial infections

were noted after the broad-spectrum antibiotics were used. Gram-positive flora of the respiratory system were frequently replaced by gram-negative bacilli ordinarily found in the intestinal tract. Bacteremia, meningitis and empyema secondary to infections by these organisms are fairly common. The most dangerous infections appear to be those of Friedländer's bacillus and pseudomonas. Evidence suggests that combinations of antibiotics may have beneficial effects in certain pulmonary and other infections. On the other hand, there is also evidence that certain of the combinations may react in the opposite manner, the combination being less effective than either antibiotic alone. Specific antibiotic resistance has been shown to be delayed by the use of drugs in combination, as in the case of the use of antibiotics in the treatment of tuberculosis. Secondary invasive microörganisms frequently complicate antibiotic therapy. Some authors have suggested that, in addition, antibiotics may cause further harm because of interference with vitamin synthesis.

Ample evidence exists in the recent literature of the severe alteration in the bacterial flora of the intestinal tract secondary to the use of antibiotics. The disturbance is not confined to those cases in which the patient was treated with the broad-spectrum type. The advantage of using these drugs to reduce the numbers of intestinal bacteria preoperatively in the case of intestinal operations is well known. 20, 58, 59 However, frequent overgrowth of such resistant organisms as pseudomonas, proteus, staphylococcus and various yeasts has posed a problem. Dearing and Heilman 31 in 1953 found that all culturable bacteria except pseudomonas and proteus were removed from the intestinal tract in the majority of patients in approximately one to six days from the start of oral Aureomycin therapy. In 1955, however, because of the emergence through the years of resistant organisms, the situation may be considerably different. Loh and Baker 20 noted that in the majority of cases the total aerobes, anaerobes and coliforms seemed to follow a similar pattern when antibiotics were used; namely, a decrease, followed by an increase during the course of medication. Di Caprio and Rantz 30 determined in 1950 that Terramycin was effective in preoperative preparation of the bowel, 3 gm. administered daily virtually eliminating the normal aerobic flora within 48 hours. The maximal effects were thought to be obtained during the first two to three days of medication; adverse effects might be expected beyond that limit of time.

Finland and Weinstein ¹⁶ observed that the organisms most frequently increased during antibiotic therapy were *Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans*. In young children, *Hemophilus influenzae* may replace gram-positive coccal infections. At the Boston City Hospital these authors studied the increasing resistance of strains of *Staphylococcus aureus* and presented evidence that for a few years after the introduction of penicillin, 85% of the strains from all sources were moderately or highly sensitive. During 1951–1952, 25% were sen-

sitive, and only two out of three strains were sensitive to Aureomycin. Less were sensitive to Terramycin.

A study of the frequency and type of infection occurring during chemotherapy was presented in 1954.¹⁴ The authors pointed out that superinfection is a common complication after the use of antibiotics. Statistics presented showed that superinfection occurred in 2.19% of 3,095 patients receiving these drugs. The organs most frequently involved were those affected by the primary disease. The organisms responsible were found difficult to treat with the antibiotics presently available. Superinfection most frequently occurred about the fourth or fifth day after starting chemotherapy. Emphasis was placed on the ability of the superinfection to con-

TABLE 2
Untoward Effects Attributable to Terramycin
Among 91 Patients with Pneumonia²⁷

(Terramycin therapy of pneumonia: clinical and bacteriologic studies in 91 patients)

Toxicity	Numer of Patients	Per Cent
None	38	42
Nausea only	4	4
Nausea and vomiting	12	13
Diarrhea, vomiting and nausea	17	19
Staphylococcus aureus predominate in fecal culture (and vomitus in 2 cases)	e 7	9
Diarrhea without vomiting	20	22
Staphylococcus aureus predominate in fecal culture Monilia predominate in stool	5 1	6
Drug rash	1	1
Stomatitis and glossitis	2	2
Severity necessitated reduction in dose	8	9
Severity necessitated changing to another agent (Aureomycin or penicillin)	10	11
Nitrogen retention	4	4

vert a benign, self-limited disease into a prolonged and even fatal one. An essential part of treatment was considered to be frequent cultural studies to determine changes in the bacterial flora. The administration of an anti-biotic effective against the predominant organism in an infection may prevent the appearance of a complicating disease. Factors which predisposed toward the development of a complicating disease or superinfection were considered to be (1) age of three years or less, (2) primary disease of the lower respiratory tract, (3) infection of the middle ear, (4) the use of a drug or combination of drugs that tended to have a broad-spectrum antibacterial effect, and (5) primary infection of the ear and secondary pneumonia.

Rantz ²¹ has described superinfections resulting from the use of antibiotics as occurring when the antibiotics suppress the normal flora of the body cavities. The way is thereby paved for the invasion by resistant organisms. This author feels that they occur more commonly in specific situations, as in the presence of obstructive disease of the urinary tract or structural disease of the lung. More common occurrence was noted in diabetics and alcoholics. Increased frequency was also thought to be present in infants and the aged, or those otherwise chronically diseased or injured. The characteristic pattern in the development of a superinfection is an initial improvement in a patient's condition after the start of antibiotic therapy, followed by a relapse. However, the intervening period of improvement may be absent.

An important contribution by Jackson et al.²⁷ discusses the complications of the use of Terramycin in the treatment of pneumonia in 91 patients. Superinfections in the lungs or the intestinal tracts occurred in all but 38

of these. Table 2 presents the statistics of this series.

In summary, superinfection or the development of antibiotic-resistant organisms appears to be the greatest hazard in the use of the antibiotics. Superinfection results from a disturbance in the normal bacterial flora of the body cavities. The reciprocal inhibitory effect is therefore destroyed or lessened. Superinfection may involve the same organ of the body in which the primary infection occurred, or a different one. Organisms hitherto unlikely to produce serious disease occasionally may cause a secondary infection more serious than the primary disease, and may sometimes cause death. These secondary infections respond poorly to known antibiotics. They occur most frequently from two to five days after initiation of antibiotic therapy, the patient appearing to have a relapse after an initial period of improvement. Frequent cultural studies are necessary to foresee or promptly recognize a serious superinfection.

Antibiotic-Resistant Staphylococci and Pseudomembranous Enterocolitis

Acute ulcerative or membranous enterocolitis in which the intestinal flora has consisted predominantly of S. aureus has been frequently recognized in recent years. Usually the situation has followed the use of the broad-spectrum antibiotics. 16 Some authors 19 have described a spruelike disturbance in which steatorrhea in association with the diarrhea was prominent. The small bowel was primarily involved, the characteristic x-ray pattern being present in three cases. The beneficial response to parenteral liver extract and vitamin B complex suggested the possibility of a vitamin deficiency resulting from alteration of the intestinal flora. Though various authors have reported an increased incidence of monilial infections in various organs after the use of antibiotics, Kligman 17 feels that most of the reported instances of serious localized moniliasis are not actually cases of the disease, and he points out the difficulty in establishing such a diagnosis. The wide-spectrum antibiotics were not found to enhance the growth of Candida albicans in vitro nor to potentiate this mycotic disease in animals. Newhauser,29 in discussing the treatment of intestinal moniliasis, concluded that the appearance of large numbers of C. albicans in the intestinal tract resulted from a change in the composition of the intestinal flora as a result of the profound effect of the antibiotics on the normal intestinal bacteria.

Anorectal side effects of antibiotics have been well described. 24, 25 Terrell and Maynard found that, of 136 patients with this complication, 125 cases followed the use of the broad-spectrum antibiotics. In 11 patients erythromycin was responsible. Diarrhea as a sole complication occurred in 37 patients, usually within 12 to 72 hours after varying amounts of antibiotics. Diarrhea and anal or anogenital pruritus occurred in 59 patients. Endoscopy showed a uniformly reddened and edematous mucosa with tiny scattered, superficial ulcerations. The mucosa was described as friable and bled on slight trauma, resembling the endoscopic picture of ulcerative colitis. Gram-stained smears from the mucosa revealed staphylococci, although the exact variety was not specified.

In 1951 Jackson et al.²⁷ summarized their experiences in the treatment of 91 cases of pneumonia with Terramycin. Particular emphasis was placed on the clinical and the bacteriologic studies. The most frequent and significant complications were superinfections with hemolytic, coagulase-positive Staphylococcus aureus. Definite involvement of the lungs occurred in four cases, one of which had a coexisting staphylococcal otitis media. Nine patients developed a severe diarrhea and stool cultures revealed pathogenic staphylococci. Most of these patients had blood and pus in their stools, and in some cases definite mucosal ulcerations were observed on sigmoidoscopic examination. In five of seven patients who died, toxic effects on the gastrointestinal tract were noted. Staphylococcal infections played an im-

portant part in the lungs as well (see table).

With regard to the development of resistance by the staphylococci, Rantz ²¹ stated that in 1943, 90% of all strains were inhibited by a few tenths of a unit of penicillin per cubic centimeter. Although this situation still prevails in parts of the world where penicillin and other antibiotics are little used, in areas of wider usage 50 to 90% of the strains isolated now are intensely resistant to this antibiotic. The more resistant strains are isolated from patients, physicians and nurses in hospitals. He reports that in a midwestern hospital experiment, erythromycin was substituted for penicillin in routine treatment of patients. Within five months, 70% of all staphylococci isolated from the upper respiratory tracts of workers there were resistant to the action of the drug, although all had been sensitive when the experiment began.

Another report, by Welch, ⁸⁸ suggests that the incidence of the antibiotic-resistant staphylococci has increased to a lesser extent than has been indicated by studies made when this organism was isolated from hospital personnel. Of 78 strains of *S. aureus* isolated from out-patients, 12.5% were resistant, whereas 68.4% of those from hospitalized patients were resistant. The importance of this organism as a potential source of infection is indicated by the fact that from 50 to 70% of normal subjects may be carriers of resistant strains. The number of resistant strains is directly proportional to the average number of people treated with each antibiotic.

TABLE 3 Summary of Case Histories

Case No. Age Sex Primary Condition	Surgery and Complications	Antibiotics Administered	Clinical Features	Remarks
L. O. 47 F. Sase ase case Leiomyomas uterus Ovarian cysts	L. oophorectomy Hysterectomy Salpingectomy	Oral and IV Terramycin, Penicillin, IM	Vomiting, diarrhea, abdominal distention, fever. Collapse state starting 7 days PO	No bacteriologic studies PM: Acute membranous enteritis (jejunum and ileum)
2 L. B. 42 M. Perforated duodenal ulcer	Closure Peritonitis Evisceration of omentum through drain opening	Penicillin and streptomycin, IM Aureomycin IV after 5 days	Nausea, vomiting, abdom- inal distention, fever, diar- rhea, collapse state 5 days PO. Oliguria, cyanosis, con- vulsions	No bacteriologic studies PM: Membranous enteritis (jejunum and ileum)
W. D. 53 M. Gangrenous appendicitis with peritonitis	Appendectomy Peritonitis Wound abscess	Penicillin and streptomycin IM Aureomycin and Terramycin IV	Abdominal distention, fever, collapse state 5 days PO Hypokalemia Hypochloremia Oliguria No diarrhea	Chronic nasal discharge. No bacteriologic studies ante mortem PM: Acute pseudomembranous enteritis (mainly jejunum and ileum, slight in colon)
E. B. 41 M. Pseudopancreatic cyst of the spleen, adherent to viscera	Removal, left diaphrag- matic hernia, atelectasis, hemothorax	Terramycin IV Penicillin and streptomy- cin, IM	Fever, respiratory embarrassment, abdominal distention. Sudden collapse and death 2 days PO	PM: Acute pseudomembran- ous enteritis (jejunum and ileum). Staphylococci on smears of bowel contents
L. S. 36 M. Duodenal ulcer with penetration	Subtotal gastrectomy pneumonitis, atelectasis (sputum showed staphylo- cocci)	Penicillin and streptomycin, IM Aureomycin, IV	Diarrhea 6 days PO. Abdominal distention, irrational, slight icterus, fever, collapse state 7 days PO	PM: Acute pseudomembran- ous enteritis (ileum). PM cultures showed S. aureus and proteus

Case No. Age Sex Primary Condition	Surgery and Complications	Antibiotics Administered	Clinical Features	Remarks
M. W. 19 F. Absees and cellulitis about third molar tooth	Incision	Penicillin IM Penicillin and streptomy- cin IM Terramycin IM Erythromycin O	Nausea and vomiting. Diarrhea 6 days after entrance. Collapse state on day of diarrhea. Fever. WBC 60,000 day of death	Postnasal discharge and nasal congestion. PM: Acute enterocolitis (ileum and jejunum, colon). Cultures of intestinal contents negative
M. C. 13 months F. Upper respiratory infection	None	Oral Terramycin. Peni- cillin and streptomycin IM	Listlessness, drowsiness, diarrhea one day (3 days after starting antibiotic at home). Dehydration, cyanosis, fever, dyspnea	PM: Acute enterocolitis (ileum, jejunum, colon). Staphylococci on microsection
J. F. 23 months F. ponths Upper respiratory infec- tion. Otitis media F.	None	Penicillin IM Streptomycin IM Erythromycin O Sulfadiazine and Terra- mycin O	Temperature to 105° F. Persistent diarrhea, hypona- tremia, decreased CO ₂ . Sud- den collapse 8 days after entrance. Twin sister pre- viously had severe enteritis. Stool cultures showed S.	PM: Staphylococcal enteritis (jejunum, ileum and colon)
9 E. E. 80 M. Fracture knee, compound	Open reduction	Penicillin and streptomy- cin IM	Diarrhea, azotemia, vomiting, irregular pulse, Cheyne Stokes respiration, sudden collapse, death 5 days after entrance	PM: Uremia due to nephrosclerosis, pseudomembranous enteritis. Stool culture revealed pathogenic S. aureus
A. G. 63 F. Intracapsular fracture, left femoral neck	Open reduction and fixa- tion. Later I and D with secondary closure	Terramycin Achromycin Chloromycetin, penicillin and streptomycin, various routes	Postop. resistant S. aureus infection with severe toxicity, successfully eliminated. Later aerobacter astreptocces infection. Bloody loose bowel movements, abdominal pain, leukocytosis, shock, hyponatremia, azetemia, death	PM: Acute necrotizing enterocolitis, associated renal and GB disease. Stool contents cultured Aerobacler aerogenes and unidentified coccus. Pathology probably related to pseudomembranous enterocolitis

TABLE 3-Continued

Case No.	Surgery and Complications	Antibiotics Administered	Clinical Features	Remarks
Frimary Condition 1. I. F. 53 M. RUL pneumonia followed by lung abscess	None prior to colitis onset. Later tube drainage of abscess	None prior to colitis onset. Later tube drainage of cin initially; later Achronabscess mycin IV and orally, sulfadiazine orally, and streptomycin IM		3rd stool smear and culture revealed stabhylococi at time of appearance of diarrhea. Prompt, effective changes in Rx instituted
12 A. O. 45 M. Acute gangrenous appendicitis with peritonitis	Appendectomy	Penicillin and streptomy- cin IM, Achromycin IV Later, erythromycin and Chloromycetin IV, strep- tomycin IM	Severe, prolonged colitis prior to vigorous required reatment after resistant S. aureus cultured from stool. Very stormy course, gradually responding to blood, changed antibiotics, 0s, vasopressors, ACTH, cortisone, and large quantities of electrolyte replacement	Prolonged period of colitiss prior to recognition by consultant caused marked depletion of the patient which was very difficult to restore. Here ACTH and cortisone were most helpful

Studies at the Boston City Hospital by Finland and Haight ³⁶ showed a significantly higher proportion of strains of fecal staphylococci were resistant to penicillin, Aureomycin and Terramycin than of strains derived from any other source. In a study of 500 strains they noted that three fourths were resistant to penicillin, one fourth to Aureomycin and one third to Terramycin. A close correlation was found between penicillin resistance and penicillinase production. ^{10, 37, 64} The strains resistant to Aureomycin and Terramycin were all resistant to penicillin, but the reverse was not true. An analogous situation with regard to the sulfonamides was found by Prissick ³² and Spink, ³⁷ who noted that these drugs were less effective against staphylococci than against other gram-positive cocci. Such strains of

staphylococci were found to produce para-aminobenzoic acid.

The importance of the antibiotic-resistant staphylococci was discussed by Spink.⁸⁷ He pointed out that the mortality rates in many clinics approach or surpass 50% in staphylococcic septicemia. One of the greatest problems is the rapidly developing resistance to the antibiotics. The organisms are quite hardy and adaptable to changing environments, and human reservoirs are great, particularly in the nasopharynx and on the skin. These factors are more prominent in hospital personnel. It has been fairly well established that when an antibiotic or sulfonamide is used promiscuously and intensively in a community, resistant strains of staphylococci will soon make their appearance and parasitize a significant segment of the population. This author feels that there is no one explanation for this antibiotic resistance among the staphylococci. The resistance is considered as an adaptation to the changed environment, with "survival of the fittest" and "natural selection" in operation. Mutants may be responsible and may occur spontaneously.

A resemblance has been noted to some cases of salmonella and cholera infection, although no enterotoxin had been demonstrated, either in the fecal contents or in the staphylococcus cultures isolated. More recently, however, Surgalla and Dack ⁶³ have been able to show that enterotoxin-producing staphylococci were present in the intestinal tract of 30 out of 32 patients with enteritis following antibiotic therapy. They suggest that enterotoxin is produced in vivo by antibiotic-resistant, food poisoning strains of staphylococci. Whereas in the ordinary case of food poisoning the enterotoxin is produced in food outside the body, with no further production in vivo, in staphylococcic enteritis following antibiotic therapy, enterotoxin may continue to be produced as long as the antibiotic suppresses the normal

flora.

The staphylococci as a cause of pseudomembranous colitis have been well documented, ^{21, 27, 31, 34, 35, 41, 42, 44, 45} although the mechanism has not been clear. The present evidence suggests ³¹ that these severe reactions occur in patients who are already ill from some disease, such as pneumonia or peritonitis, or who have had a major operation.

The staphylococcus in certain instances has been known to produce extracellular substances or exotoxins ^{87, 68} which have produced both respiratory and circulatory collapse. This exotoxin is antigenic, and an antitoxin can be produced against it. The same exotoxin can produce severe skin necrosis. This organism also produces enterotoxins which may cause severe diarrheal attacks when ingested (the so-called "food poisoning"). An erythrogenic toxin has been described which is similar to the rash-producing toxin of scarlet fever. Streptococcic antitoxin is said to neutralize the staphylococcic erythrogenic toxin. It seems very probable that some toxin elaborated by the antibiotic-resistant staphylococci acts as an irritant, producing the pseudomembranous reaction in the intestinal tract in a manner analogous to the reaction occurring in true bacillary dysentery.

A report ⁴² of two fatal cases of pseudomembranous staphylococcal enteritis has been presented. One case revealed that "the jejunum and ileum were lined by a continuous yellowish-tan fibrinous pseudodiphtheritic cast which could be lifted intact." A culture from this membrane revealed hemolytic staphylococci and *Pseudomonas aeruginosa*. Another similar case revealed *S. aureus*. It was thought that the organisms might be washed, swallowed, or carried by a Levine tube into the gastrointestinal tract from the upper respiratory tract. Nose and throat cultures were suggested by the authors, to be taken prior to and during antibiotic therapy, to identify the predominant bacteria and aid in the choice of an antibiotic.

The emergence of antibiotic-resistant staphylococci producing enteritis is not limited to the use of Aureomycin, Terramycin or chloramphenicol. Kramer 35 in 1948 reported a fatal case after oral streptomycin therapy. He thought that a patient receiving the drug orally might absorb enough of this material to render organisms remote from the intestinal tract resistant, thus producing a focus of resistant pathogens capable of reaching the gut and multiplying there. Susceptibility in infants was thought to be greater because the bactericidal action of the gastric secretions is less than in an adult. Fairlie et al.34 reported three cases following combined penicillin and streptomycin therapy. They believed that the simple suppression of the intestinal flora was not a sufficient explanation for the overgrowth by staphylococci or other organisms. Other explanations were thought to be that there was an introduction of a particular strain of staphylococcus from a different area, or that there was a direct stimulation of toxin production under antibiotic influence. It is known that certain antibiotics are capable of stimulating the growth of bacteria in vitro. These authors feel that the condition should be considered not as a staphylococcal enteritis, but as a toxic state resulting from a disturbed intestinal ecology.

Although several authors have advised the introduction of erythromycin in the treatment of staphylococcic enteritis as soon as this condition is suspected or diagnosed, one cannot rely entirely on this drug because evidence has been presented of the rapid development of resistance by the staphylococci.61 Some authors 88 have noted a sizable decrease in the frequency of complicating diarrhea and gastrointestinal disturbances when Terramycin and Aureomycin are used in smaller dosages. The clinical and bacteriologic results were little different. They also noted that in many cases diarrhea and the staphylococci cleared after the antibiotics were stopped, suggesting a question as to the efficacy of erythromycin when instituted. However, in their cases penicillin was usually started to continue treatment after the broad-spectrum antibiotics were stopped. Forty-one per cent of 91 pneumonia patients treated with Aureomycin or Terramycin suffered a diarrhea with a dosage level of 500 mg. every four hours. S. aureus predominated in the feces of 18 patients who had diarrhea and for whom cultures were done. Another study 81 found that the substitution of erythromycin for Terramycin or Aureomycin produced a prompt disappearance of the untoward symptoms and the staphylococci from the intestinal tract. These authors, in general, have given up the use of Terramycin and Aureomycin in the preoperative preparation of patients to undergo intestinal surgery because of the existence of the antibiotic-resistant strains of staphylococci. It is recommended that if these antibiotics have been used preoperatively, cultures of the intestinal contents at the time of operation be taken to rule out the presence of staphylococci in large numbers. Neomycin alone or combined with Terramycin for short periods has been recommended more recently.58,59

Full dependence cannot be placed on erythromycin for effective treatment of all staphylococcic infections. Haight and Finland 49 found that the resistance of this organism to the drug developed at about the same rate as that to penicillin. However, a case was cited of a young Negro who had received Terramycin and penicillin for pneumonia, who developed a severe enteritis and whose stool was positive for staphylococci. When these drugs were omitted and erythromycin was given, the stools promptly became soft and formed, and staphylococci could no longer be found on stool culture. Other authors 46 who attempted to determine the incidence of erythromycinresistant staphylococci found that in December, 1952, and in March, 1953, no strains were resistant, whereas in March, 1954, seven of 100 strains were resistant. They felt that a reservoir of antibiotic-resistant staphylococci existed in carriers, particularly among hospital personnel. In most cases the antibiotic-resistant organisms were recovered from the intestine, postoperative wounds or urine after urologic operations or catheterization. Because of the increasing incidence of erythromycin-resistant organisms, one should use the drug only when definitely indicated in serious infection.

That erythromycin may in itself cause gastrointestinal irritation was noted by Herrell and his associates,⁴⁷ who studied 54 patients with staphylococcic infections, eight of whom had septicemia. These organisms were in most instances relatively insensitive to penicillin, streptomycin, Aureomycin and Terramycin. In six cases erythromycin proved life-saving, bac-

terial resistance developing rather slowly. Two cases showed rapidly developing resistance and were classed as failures.

In summary, one may conclude that staphylococci play a major rôle in the development of severe pseudomembranous entercolitis because of their marked adaptability to the antibiotics, in contradistinction to the normal intestinal flora. Good evidence exists that the actual source of these resistant organisms is probably in carriers, in a community or hospital where many individuals have been subjected to the promiscuous administration of antibiotics, particularly those with a focus of infection in the nasopharynx. The staphylococcal enterotoxin very probably leads to the formation of a pseudomembrane by its direct irritant action, as well as producing generalized systemic effects. Although erythromycin offers a great deal of help in treatment, we are seeing gradual development of resistance to this drug by the staphylococci.

CLINICAL FEATURES

Attention has been called to certain features in the discussion of the cases presented. Perhaps the most important general pattern noted is the presence of relapse after an initial period of improvement in a patient being treated with antibiotics for one of a variety of conditions. Improvement initially need not occur, the complication being associated with or engrafted onto the primary condition being treated. A sudden rise in temperature after an afebrile period may occur. 9, 10, 11, 27, 39, 44 Associated lethargy, mental aberrations, nausea, vomiting, hiccups, abdominal distention, pain, diarrhea and collapse most frequently occur rather rapidly. Abdominal distention has been ascribed to paralytic ileus. There have been no x-ray findings peculiar to this condition, and in most cases the pattern of ileus is evident. The majority of patients have diarrhea, which may be of very sudden onset and explosive in character, and the feces may contain blood and pus. 27 In some patients a cast of the intestine may be passed which, in reality, is the sloughed pseudomembrane.

The presence of diarrhea is not invariable in this type of enterocolitis. ¹⁰ Its absence has been ascribed to the presence of an adynamic ileus as well as to a sudden onset, so sudden, in fact, as to cause a severe outpouring of fluid material into the intestinal lumen with marked dehydration and collapse and death before diarrhea has occurred.

The outpouring of fluid, either with or without diarrhea, leads to hemo-concentration, azotemia, oliguria, changes in acid-base balance, and electrolyte disturbances. Finally a state of collapse appears, usually with signs of vasomotor paralysis, which in the majority of cases is irreversible, particularly when prompt and vigorous treatment is not instituted. One may ascribe the terminal state to the combined effects of toxemia, and in many instances of the associated primary disease or operation. It appears likely that adrenal failure may be the greatest terminal factor.

In summary, when one is confronted with an apparent relapse during the course of an illness, injury or postoperative state, whether or not antibiotics have been used in treatment, one should consider enterocolitis as a possibility. If signs of diarrhea, paralytic ileus, fever, dehydration, loss of blood volume and collapse are present, stronger suspicion is in order and prompt, vigorous treatment is necessary. Reports from many sources indicate a rising index of suspicion, inasmuch as more cases are being diagnosed ante mortem and reports of successful treatment are appearing.⁶⁴ Awareness and timely treatment will undoubtedly bring more successful results.

PREVENTION AND MANAGEMENT

This article will not include specific therapeutic recommendations in minute detail regarding prevention and management, since therapy will depend on the type of primary condition present, as well as on many other factors. Generalizations on certain principles which may be effective in prevention and management, based on the experiences of many authors, will

be considered and presented here.

Good medical and surgical technics are most important in caring for a primary disorder, whether or not antibiotics are used. Evaluation of the patient with regard to physical condition, age, associated disorders and other variables which might influence resistance is of importance. Medical problems involving chemical intoxications, either organic or inorganic, as well as bacterial intoxications must be considered in the light of present knowledge. Accepted surgical principles should be observed in the treatment of intestinal obstruction to prevent fecal stasis, mechanical pressure and dilatation, whether on an advnamic or a dynamic basis. If shock can be considered a cause rather than an effect of a severe membranous reaction, its prevention or early treatment will be beneficial. Since the non-antibiotic type may occur in response to a wide variety of stimuli or toxic agents, it would be practically impossible to suggest concisely specific measures in prevention and treatment. One must, however, consider particularly the lethal or sublethal systemic effects of such factors as respiratory embarrassment, loss of plasma volume, stasis of blood in the lower extremities and intestine, electrolyte disturbances, cardiac disease and associated infections, perhaps unrecognized.

In those cases of enterocolitis related to the use of antibiotics, whether surgical or nonsurgical, preventive principles may be followed with regard to (1) development of antibiotic resistant organisms, particularly staphylococci, and (2) the detection of resistant organisms before severe untoward reactions occur. Antibiotics should not be used promiscuously or indiscriminately, nor should they be relied upon to prevent complications resulting from poor medical judgment, inexpert surgical technic, or faulty asepsis. Insignificant infections or those known not to respond to anti-

biotics, and those which run a limited course, may well be observed prior to treatment with antibiotics, symptomatic treatment being rendered until such time as real need of an antibiotic may arise. In certain instances, as in prophylaxis of rheumatic fever, preventive antibiotic use is warranted.

Huge amounts of antibiotics are being used each year.^{21, 24} Care has been recommended in the use of the broad-spectrum variety in preparation for intestinal surgery.³¹ Nose and throat cultures with sensitivity tests may be of particular benefit in discovering latent resistant staphylococci.^{44, 42} Preparation of direct smears early and frequently from the intestinal contents, the incision, or the respiratory tract is encouraged.³⁴ If staphylococci appear to dominate the picture, one should not wait for cultures and sensitivity tests before changing antibiotics. It is likely that if more cultures had been taken, using media and conditions likely to demonstrate pathogenic staphylococci, many more proved cases of staphylococcal enteritis would have been diagnosed. When one contemplates the use of an antibiotic, if time permits, isolation and identification of the organism with its sensitivities are most important.

Since the duration of use and the dosage of antibiotics are directly proportional to the development of pseudomembranous enterocolitis, 45, 20, 14 one may conclude that the smallest acceptable dosage should be used and only for that period deemed necessary. Suspicion should immediately be aroused

by longer use or larger dosage.

Close observation is very important with respect to specific signs and symptoms which might lead one to suspect a pseudomembranous enterocolitis. A sudden rise in temperature, abdominal distention, vomiting or diarrhea should be cause for alarm. A membranous cast may actually be passed. A patient may die before there has been time for diarrhea to occur.⁴⁸ Aureomycin given intravenously may be excreted into the bowel.^{18, 58} Also, parenteral administration of combined penicillin and streptomycin does not preclude the development of this entity.

In the active treatment of known staphylococcal enteritis, attention has been called to stopping promptly the offending antibiotic and substituting erythromycin on the basis that the latter may be more effective, with less chance of resistance. Other antibiotics may be substituted as well. However, one should not lose sight of the rapidity with which resistance may be developed toward the new drug. Judgment will determine the amounts of drugs deemed necessary, but aggressive treatment must be carried out in the fulminating case. Combinations of bacitracin with penicillin have been used where good renal function prevails.³⁷ Various other combinations are possible when sensitivity tests have shown their effectiveness.

Fluid and electrolyte replacement with plasma, blood and fluids containing specific electrolytes is essential in combating shock, dehydration and loss of electrolyte, as well as hemoconcentration. Such vasopressor substances as norepinephrine may be useful here, particularly in the cases showing

sudden fall in blood pressure. Corticotropin and the adrenal corticosteroids have been reported as useful in this situation.⁴⁵ Adrenal cortical extract may have some use.

In general, prompt vigorous treatment is necessary if one is to benefit the patient in the collapse phase. This state is most commonly irreversible.

CASE REPORTS

Case 1. On December 17, 1953, a 47 year old Negro female underwent an abdominal hysterectomy, left oophorectomy, and salpingectomy because of pelvic inflammatory disease, leiomyomas of the uterus and follicular cysts.

Preoperative preparation had included Terramycin orally. Her immediate postoperative course was uneventful. Terramycin was continued intravenously. On



Fig. 1. Case 1. A portion of the ileum showing pseudomembrane formation, and another portion showing none.

December 20, 1953, moderate abdominal distention was present but peristalsis was good. Fever occurred on the following day and continued intermittently. On December 24, 1953, collapse developed, with rapid pulse and respiratory rates, unobtainable blood pressure, wheezing respiration, gallop rhythm, increased abdominal distention, diarrhea, and almost complete disappearance of peristaltic sounds. During the ensuing eight hours the patient's temperature rose to 104.4° F. rectally, and the respirations became more rapid and shallow. The pulse was faint at 150 beats per minute, and the blood pressure remained unobtainable. The abdomen was distended and silent, and the patient vomited around a suction tube. Vasopressor drugs and blood volume expanders were used, without benefit. Penicillin was started in large dosages. Diarrhea appeared. Abdominal distention increased. The temperature rose to 106.2° F. rectally, and the patient died in a septic, shocklike state about 19 hours after the onset of collapse. No bacteriologic studies were made.

Autopsy Report: The cause of death was attributed to acute membranous enteritis of the jejunum and acute enteritis of the ileum. Contributory causes of death were cortical necrosis of the kidneys and hypostatic lobular pneumonia.

Grossly, there were fibrinous deposits over the surface of the small bowel, with thickening of the wall. No bowel obstruction was noted. A thick yellowish gray membranous lining of the entire jejunum was noted. The membrane was easily removed from the mucosal surface, revealing it to be red and injected. The terminal ileum revealed no membrane formation, but the mucosa was acutely congested. No inflammatory reaction was present in the large bowel. On microsection, the ileum showed considerable degeneration of the mucosa, with absence of epithelial elements and profound congestion of the mucosa and submucosa. The serosa was edematous. The jejunum showed destruction of the mucosa, with only an occasional glandular element present along the basal aspect. The remainder of the mucosa was replaced by an inflammatory exudate that contained many lymphocytes and neutrophilic leukocytes. The entire wall was edematous and infiltrated with lymphocytes. The process extended out to the serosa. Many masses of bacteria were scattered throughout the superficial aspect. The adrenal glands showed granularity and vacuolation of the cells of the cortex. In some instances the cells showed autolysis of the nuclei and cystic degeneration of the cytoplasm.

Comment: After preoperative use of a broad-spectrum antibiotic for residual pelvic inflammation, continuation by the intravenous route apparently led to an acute membranous enteritis which was not recognized promptly. Bacteriologic studies might well have been a warning. Although the staphylococcus was not conclusively demonstrated, one can assume that it was implicated. The terminal state of collapse, occurring two days postoperatively, lasted about 19 hours and did not respond to treatment.

Case 2. A 43 year old male mechanic with a history of a peptic ulcer since 1934 underwent operation on July 15, 1954 for closure of a perforated duodenal ulcer. The preoperative findings had included signs of free air under the diaphragm, peritoneal contamination and evidence of shock. Postoperative suction, blood transfusions and parenteral fluids were administered. Combined penicillin and streptomycin therapy was given in large dosages intramuscularly. For three days after operation the patient remained distended and passed no flatus. At this time his temperature rose to 102.4° F. rectally, and he passed a small greenish liquid stool. Distention of the abdomen increased, and nausea and vomiting occurred. He passed several yellowish and greenish brown liquid stools with large amounts of mucous shreds and blood. Vomiting and abdominal distention continued. On July 20, 1954, operation was performed to relieve an evisceration of a portion of the omentum through a drain opening. Shortly thereafter a state of collapse appeared, with a cardiac rate of 160 to 180, unobtainable blood pressure and shallow rapid respirations. At this time the patient received Aureomycin intravenously. Supportive treatment was instituted, but output of urine declined, diarrheal bowel movements persisted, the temperature rose to 106.4° F. rectally, and a convulsion occurred. The patient quickly became irrational and cyanotic, and died. No bacteriologic studies were made.

Autopsy Report: Examination revealed evidence of a paralytic ileus, toxic hepatitis, toxic glomerulonephritis, pleural adhesions, and toxic degeneration of the heart, liver, spleen and kidneys. The entire small bowel was greatly distended, the wall was edematous, and the lumen was filled with yellowish fluid. In the proximal portion "curdled" material resembling milk or milk products was present. A fibrinous deposit covered the mucosa, which was noted to be more prominent over the jejunum. The ascending and transverse portion of the colon was distended, and

the descending portion was collapsed. Microscopically, the mucosa was intact. The lumen contained a large number of neutrophils. A cellular infiltration of the mucosa was observed, the submucosa was edematous, and considerable congestion was present. Large masses of bacteria were present in the neutrophils. The adrenals revealed a marked congestion of the sinuses. The cells in the cortex were granular and vacuolated. The cells of the medulla were hyperchromatic, and the cytoplasm was granular and vacuolated.

Comment: The offending antibiotic in this case was a combination of penicillin-streptomycin. Diarrhea occurred three days postoperatively and collapse two days later. "Mucous shreds" passed were probably portions of disintegrated pseudomembrane which appeared as "curdled" material in the bowel lumen at autopsy. Again, bacteriologic studies would have been important. Peritoneal contamination was present, which probably influenced the development of ileus.

Case 3. A 53 year old white male underwent operation on March 8, 1954, after a 24 hour history which was typical for appendicitis. The patient had suffered from chronic sinusitis, and on examination showed chronic nasal inflammation, obstruction and mucoid discharge. A gangrenous appendix and extensive peritonitis were found at operation. Postoperatively the patient received intragastric suction, intramuscular penicillin and streptomycin, and parenteral fluids. Distention and fever persisted after operation. On March 15, 1954, a superficial wound abscess was drained. Signs of peritonitis continued. Parenteral feedings and antibiotics, including intravenous Aureomycin, were continued. The following day the urinary output decreased markedly and a shocklike state appeared, associated with a rapid rise in temperature to 105.4° F. rectally. The blood pressure became unobtainable, abdominal distention increased, and the patient became cyanotic. At that time laboratory studies revealed the presence of a hypochloremia, severe hypokalemia, hemoconcentration, and a normal carbon dioxide combining-power. Blood transfusions, intravenous Terramycin, aqueous adrenal cortical extract, stimulants and parenteral potassium were administered. On March 17, 1954, the temperature continued to rise, to 106.6° F. rectally, the heart tones became barely audible, and oliguria increased. A mottled cyanosis appeared, the patient became restless, and his blood pressure was unobtainable. Cheyne-Stokes respiration became prominent and the patient died, having shown no response to restorative treatment. Diarrhea did not occur during his hospital course. No antemortem bacteriologic studies were made.

Autopsy Report: Death was attributed to acute pseudomembranous enteritis with paralytic ileus following appendectomy for acute appendicitis. Contributory hypokalemia was present. Grossly, the entire small intestine was distended with gas and fluid, which contained a large amount of yellowish white mucus and exudate in shreds, and thin sheets which stripped off the mucosal surface very readily in the jejunum and upper ileum, leaving a smooth gray-pink mucous membrane. In the lower small bowel, where the fluid content was somewhat less, the membrane was more compact and adherent to the surface of the intestine, although even in this portion it could be stripped readily. Small patches of exudate were noted on the ascending colon. Microscopically, an accumulation of a compact exudate was noted on the mucosal surfaces, composed of fibrin and leukocytes, mostly degenerating. Desquamation of the superficial epithelium was noted, but no profound changes were noted in the deeper portions. Plasma cells, lymphocytes and eosinophils were seen to infiltrate the stroma. No polymorphonuclear leukocytes were seen, in contrast to

the large numbers seen in the surface exudate. The vessels of the submucosa were congested. In some areas the exudate on the surface of the mucosa contained dense colonies of bacteria which appeared to be cocci, although some bacillary forms were also visible. No bacteria were seen in the tissues of the intestinal wall, even in the mucous membrane. The adrenal glands showed compactness of the cortical cytoplasm. Some individual cell dissociation was present but no extensive disintegration. Focal necrosis was present in the inner cortical zone, one area of necrobiosis being noted in the cortical epithelium.



Fig. 2. Case 3. A portion of the ileum showing pseudomembrane formation in the small intestine.

Comment: The presence of chronic sinusitis suggests the possibility of an existing carrier focus for staphylococci, but no proof is offered because no bacteriologic studies were made. Peritonitis undoubtedly contributed to the ileus, which perhaps influenced the development of a pseudomembranous inflammation. It is noteworthy that diarrhea did not occur, but perhaps this was the result of persistent ileus.

Case 4. Operation was performed on a 41 year old white male steel-handler on November 15, 1954, for the removal of a large pseudopancreatic cyst involving the spleen. The removal was difficult because of adherent viscera. The mass had caused secondary atelectasis of the left lung through elevation of the left hemidiaphragm. A postoperative diaphragmatic hernia developed, with an associated hemothorax. On November 16 and 17, 1954, the patient did not do well, showing a rising temperature, respiratory embarrassment and abdominal distention. Intravenous Terramycin was administered after operation, as well as intramuscular penicillin and streptomycin. Postoperative abdominal x-rays were compatible with an adynamic ileus. On November 17, 1954, the pulse rate reached 136 per minute, the temperature increased to 104.0° F., and respiratory difficulty increased. No diarrhea oc-

curred. A total of 6,500 c.c. of whole blood was used in supporting the patient, maintaining a blood pressure of 136/70 mm. of Hg. However, on this date, as the

patient was being turned in bed, he suddenly died.

Autopsy Report: Death was attributed to acute pseudomembranous enteritis, with a contributory cause listed as postsurgical diaphragmatic hernia with left hemothorax. Grossly, the jejunum and ileum contained a thin, opaque yellow fluid in which was suspended a stringy pseudomembrane adherent but readily detached from the surface of the mucosa. When it was pulled away, a slightly reddened mucosal surface was seen, but with no focal lesion. This material was thicker and more tenacious in the ileum, having a grayish green color and although soft and mucoid in appearance, it was adherent to the mucous membrane. The large bowel contained a light brown, semi-fluid stool. Microscopically, the small bowel showed marked inflammation of the mucous membrane. In some areas there was submucosal involvement, with a light sprinkling of inflammatory cells. Some sections showed the mucous membrane to be covered by a coating of purulent exudate containing some fibrin, the surface epithelium being largely desquamated, leaving the glands well preserved. Polymorphonuclear leukocytes, lymphocytes and plasma cells infiltrated the stroma of the mucous membrane. Polymorphonuclears were more numerous. Congestion of the mucosal and submucosal blood vessels was noted, but they appeared patent. Bacteria were not present in the routine by stained sections. Smears prepared from the material showed colonies of staphylococci.

Comment: The patient apparently underwent considerable intra-abdominal surgical trauma, which perhaps contributed to his fatal outcome. It is interesting to note that no diarrhea occurred and that only parenteral antibiotics were used. A pseudomembrane formed which showed staphylococci, yet no suggestive signs of warning were present.

Case 5. A 36 year old white male machinist underwent a subtotal gastric resection on November 1, 1954, after repeated unsuccessful attempts at medical control of a duodenal ulcer over a period of four to five years. On this admission, evidence of a subacute posterior perforation was present and was confirmed at operation. The floor of the ulcer was found to be composed of inflamed pancreatic tissue. Postoperatively, the usual measures were used. Penicillin and streptomycin were administered intramuscularly. On November 2, 1954, thick and tenacious pulmonary secretions appeared. On November 4, 1954, the patient's temperature was elevated, and a bedside x-ray revealed a bilateral elevation of the diaphragm, questionable atelectasis, and some infiltration at the base of the right lung. On November 7, 1954, diarrheal bowel movements appeared, the abdomen being moderately distended but soft. Penicillin and streptomycin were continued. At this time the serum electrolytes were reasonably normal. Another bedside film showed the chest to be improved. However, the diarrhea became much more severe, there was loss of copious amounts of fluid from the duodenal tube, and the patient became extremely irritable. Vomiting occurred. Intravenous Aureomycin was administered, as well as parenteral potassium and other electrolytes. On November 8, 1954, the patient was very restless and irrational, the pulse rate reached 136 per minute, and a slight icterus became apparent. The blood pressure at this time was 104/80 mm. of Hg. As time went on the restlessness was replaced by lethargy, cyanosis, tremors and hypotension. The pulse and blood pressure became unobtainable, and the temperature rose quickly to 108° F. rectally. The patient became comatose and died. On November 4, 1954, a sputum culture showed the predominant organism to be Staphylococcus aureus. Postmortem cultures of the intestinal contents revealed S. aureus and proteus.

Autopsy Report: Death was attributed to acute pseudomembranous enteritis

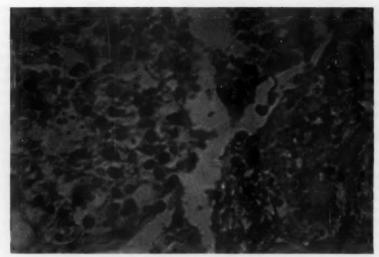


Fig. 3. Case 5. A microsection showing mucous membrane on the left and pseudomembrane on the right.

following gastric resection. Grossly, the small intestine below the anastomosis showed moderately uniform dilatation. The lumen was filled with an opaque, grayish yellow watery fluid which contained strands of mucus and fibrin. The full length of the small intestine was covered by a yellowish white exudate of mucopurulent appearance which was moderately adherent to the mucosal surface. No ulceration or

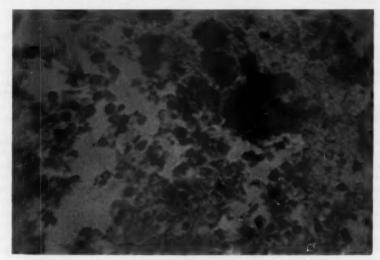


Fig. 4. Case 5. A microsection showing colonies of staphylococci in the pseudomembrane.

other focal features were found. The large intestine showed a similar change in the ascending and transverse portions. Microscopically, the intestine showed a desquamation of the surface epithelium. The interstitial tissue of the mucous membrane showed a uniform, diffuse infiltration of mononuclear inflammatory cells, with lymphocytes and plasma cells predominating. In some sections, submucosal edema was evident, and a light inflammatory cell infiltrate was seen. An exudate covering the mucosal surface was seen to be composed of a compact mixture of neutrophils, fibrin, cellular debris, and colonies of deeply stained bacteria having staphylococcal arrangement. These organisms were extremely abundant and were confined to the very surface of the pseudomembranous exudate; moreover, where the large numbers of polymorphonuclear leukocytes were abundant, the immediately underlying mucous membrane still preserved a picture of lymphocytic and plasma cell reaction with very limited numbers of polymorphonuclears. The adrenal glands showed some vacuolation of the glomerular zone, with lipoid depletion and some tendency to pseudogland formation.

Comment: This patient had considerable peritoneal soiling which would probably contribute to the development of an ileus. Staphylococci were found in the sputum as well as in the feces prior to death, and it is logical to assume that the lung was a site of infection with antibiotic-resistant organisms. Diarrheal bowel movements gave the attending physician warning as to the possibility of enteritis as a dangerous complication. A complicating alcoholism may in some way have contributed to the lack of resistance on the part of the patient. Broad-spectrum antibiotics were not used early in this case, and the combined penicillin and streptomycin given were administered parenterally.

Case 6. A 19 year old housewife was admitted to the hospital on October 29, 1954, because of severe cellulitis and abscess formation near a lower left third molar tooth. Treatment prior to hospitalization had included an unspecified amount of intramuscular penicillin, and the soft tissue had been incised. In spite of this treatment the cellulitis had become more severe. The patient earlier in the year had suffered an attack of acute rheumatic fever. Preliminary laboratory and x-ray examinations revealed no unexpected findings. Analgesics, and penicillin combined with streptomycin intramuscularly, as well as intramuscular Terramycin, were administered, the latter being changed to an oral preparation later. Slight improvement in the patient's condition was noted after about 48 hours and, although slight nausea and vomiting occurred, the abdominal findings were not considered alarming. The following day, midabdominal and epigastric tenderness were noted, but the abdomen remained soft. On November 5, 1954, nasal congestion was present, and later a thick, stringy, postnasal drip. The temperature rose to 105° F. orally. Although the throat appeared red, the edema and induration about the involved tooth were less. On this date a large liquid defecation occurred, which was followed by other liquid, yellowish brown involuntary stools. The extremities became mottled. Erythromycin was started, penicillin and streptomycin were continued, and adrenal cortical steroids and whole blood transfusions were administered. By the following day, November 6, 1954, the temperature had increased to 105.8° F. rectally. Tachycardia to 152 per minute, tachypnea, and a drop in blood pressure to 60/40 mm. of Hg had occurred. Moderate abdominal distention and tenderness were present. Loose stools persisted and contained much mucus. Restorative treatment was not availing, and on November 7, 1954, a mottled cyanosis appeared and the patient died in a state of shock. Shortly before death the leukocyte count had reached 60,000 per

cubic millimeter, and on the day of death there was a marked drop in temperature to normal.

Autopsy Report: The primary cause of death was acute enterocolitis. Grossly, the small intestine was moderately distended throughout its entire length and contained dark greenish fluid. The intestine showed a smooth surface with flattened folds and a mild degree of vascular injection, more pronounced in the ileum, where there were poorly defined areas of reddening. The large bowel showed the same features, with a fluid content and a dull reddish discoloration to the mucous membrane. Cultures of the blood and intestinal contents were negative. Microscopically, there was a patchy erosion of the surface epithelium, with a retention of the glandular structures within the mucosa. The tissue was edematous and showed a moderate cellular infiltrate of predominantly mononuclear cells and lymphocytes, and some plasma cells. There was no exudate remaining on the surface, and the deeper

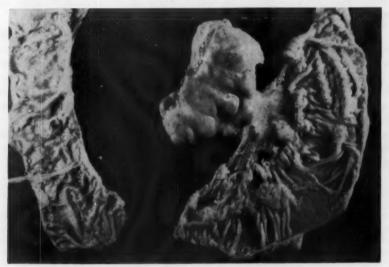


Fig. 5. Case 7. A portion of the ileum of a 13 month old child showing pseudomembrane.

tissues were not involved by an inflammatory reaction, except for the edema and light infiltrate of the submucosa. The adrenal glands showed some cellular dissociation in the cortex, which was irregular and vocuolated, and the remainder of the cell cords were depleted of lipoid. Marked vascular engorgement occurred in the inner zone, and some necrosis of the cortical cells was present.

Comment: The presence of a stringy postnasal drip in the course of this patient's illness seems significant, and it is very possible that the naso-pharynx was either the source of antibiotic-resistant staphylococci or at least an additional associated focus of these organisms. In this case active restorative treatment again failed to correct the shock. Cultures of the intestinal contents failed to reveal pathogenic staphylococci.

Case 7. A 13 month old white female was admitted to the hospital on November 28, 1954, because of diarrhea and vomiting over a 24 hour period. On November 25,

1954, treatment of an upper respiratory infection had been started at home by the family physician. Terramycin had been administered orally. Telephoned reports had indicated that the child had shown initial improvement and had done well until the day of admission to the hospital. On entrance the child was listless and drowsy and had a high fever and tachycardia. There were evidences of marked dehydration and high fever. The heart and lungs revealed no abnormality. The child persistently passed yellowish green diarrheal stools. No laboratory or x-ray examinations were completed. Parenteral fluids and penicillin combined with streptomycin were administered immediately. About two hours after admission a gradually increasing cyanosis was noted and breathing became labored. Stimulants and artificial respiration were administered without benefit, and the child died almost immediately.

Autopsy Report: Death was attributed to acute enterocolitis (staphylococcic). Grossly, the entire small bowel was filled with a watery fluid in which were suspended flakes of fibrin and a mucinous substance. The mucous membrane was covered with a similar material and was pale rather than red. The large bowel showed a similar though less pronounced change. Microscopically, a diffuse inflammatory reaction was seen to involve the mucosa, with increased cellularity between the mucosal glands. Desquamation of the surface epithelium was prominent, but generally there was a retention of gland structures. Covering the surface were patches of exudate which consisted of a mixture of fibrin and cellular debris with leukocytes. Scattered through this substance were many colonies of staphylococci. In some areas the exudate was completely lost, but elsewhere it was adherent to the surface and seemed to merge with the inflammatory constituents of the lamina propria. The adrenal glands showed no changes.

Comment: The flakes of fibrinous and mucinous substance found in the intestinal contents at autopsy were probably disintegrated pseudomembranous exudate. The age of the patient perhaps serves as a warning, inasmuch as various writers have pointed out an increased incidence in the very young and the aged. The use of a broad-spectrum antibiotic in this case in a minor upper respiratory infection without closer observation might be criticized.

Case 8. A 23 month old white female was admitted to the hospital on April 15, 1954, because of high fever. About one week before she had developed an upper respiratory infection, with nasal discharge, redness of the tympanic membranes and fever. Daily penicillin injections were given by her family physician on three days prior to admission. The temperature continued to rise daily to 105° F. orally. A twin sister had been critically ill a short time previously with a severe episode of gastroenteritis. The initial laboratory examinations, including an electrocardiogram, were not remarkable. After entrance the patient continued to receive penicillin parenterally, followed three days later by erythromycin and sulfadiazine orally. The following day streptomycin was administered. Streptomycin was discontinued on the sixth hospital day and sulfadiazine on the seventh day. Terramycin was administered then for three days, On April 21, 1954, a stool culture showed Staphylococcus aureus, Escherichia coli and Aerobacter aerogenes. A remittent fever occurred each day. Diarrhea was present during her hospital stay. Gradually the temperature approached normal and the child seemed improved. However, on April 23, 1954, she suddenly showed evidence of collapse, with cold, clammy skin and perspiration. Restorative measures were without benefit, and the child died the following day. Prior to death there was evidence of hyponatremia and decreased carbon dioxide combining power.

Autopsy Report: Death was attributed to acute enteritis due to S. aureus. Contributory factors were dehydration and interstitial pneumonitis. Grossly, the small bowel contained only small patches of mucoid material, some of which was slightly turbid. The mucosa was congested, but no membrane was seen. The large bowel was practically empty, showing no gross inflammatory reaction. Microsection showed a few neutrophilic leukocytes within the mucosa and over the surface. No ulceration was seen. The appearance of the large bowel was similar. No particular changes were noted in the adrenal glands.

Comment: This is another case in a very young child with possible foci of antibiotic-resistant staphylococci in the nasopharynx and ear who did not receive a broad-spectrum antibiotic initially. It is interesting to postulate that the patient's twin sister possibly served as a carrier, having suffered a severe staphylococcic enteritis some time before.

Case 9. On April 11, 1955, an 80 year old white male was admitted to the hospital after he had sustained a compound fracture of the left knee when he was struck by an automobile. He had a history of hypertension and had had a gastric resection years ago. An open reduction of the fracture was performed on the day of entrance. The patient received daily penicillin and streptomycin intramuscularly. His course was satisfactory until April 15, 1955, at which time loose stools appeared, as well as a slight icterus. He was not in acute distress and there was no fever, nausea or vomiting. The abdomen remained soft and nontender. On April 16, 1955, the patient was in no severe distress until about 7:00 p.m., when he was found in extremis, with rapid respirations, hypotension, moist râles in the lungs, and a uremic odor to the breath. The nonprotein nitrogen of the blood on the last day measured 104 mg. %. The patient vomited, exhibited Cheyne-Stokes respiration and an irregular pulse, and died almost immediately. Stool cultures were obtained prior to death, and the diagnosis of pseudomembranous enteritis was entertained ante mortem.

Autopsy Report: Death was attributed to uremia due to advanced nephrosclerosis and pseudomembranous enterocolitis. Grossly, the mucous membrane of the small bowel revealed an extensive yellowish pseudomembrane which was rather easily detached from the pink mucosal surface. The content of the bowel was fluid and yellowish. The large bowel contained a thin, soft, yellowish stool, but no membrane formation or ulceration. Microscopically, the section of the small intestine showed a fairly intact mucous membrane with some desquamation of the surface epithelium. There was a covering of exudate consisting of fibrin and desquamated cells, a moderate number of leukocytes, and a large number of cocci in solid colonial masses. The inflammatory process did not appear to penetrate very deeply into the mucosa. Relatively few cells were present in the submucosa, although some of the folds showed edematous submucosal tissue. A culture of the stool contents at autopsy revealed beta hemolytic, coagulase-positive Staphylococcus aureus and Escherichia coli.

Comment: This aged man evidenced uremia due to nephrosclerosis. Uremic colitis has been known to result in the formation of a pseudomembrane in the intestine. However, penicillin and streptomycin were used in treatment of the compound fracture, and the patient developed a sudden shock-like state which was irreversible, suggesting the likelihood of a pseudomembranous enteritis resulting from the use of antibiotics.

Case 10. This 63 year old white housewife suffered an intracapsular fracture of the left femur on December 12, 1954, and underwent operation for hip fixation the

following day. Her postoperative course was febrile but blood cultures were negative. On December 21, 1954, the infected hip wound was drained and a coagulase-positive Staphylococcus aureus culture was obtained which was resistant to most of the antibiotics. However, after a trial of various other broad-spectrum antibiotics, Chloromycetin was of benefit and seemed to overcome the infection. A secondary closure was performed on January 20, 1955, and the patient was discharged on February 14, 1955.

The patient was re-admitted on February 17, 1955, because of a recurrence of inflammation in the wound. She was suffering from pain and fever, and showed a leukocytosis. She was dehydrated and vomiting. The pulse was rapid and the leg was indurated. On February 22, 1955, the leg was incised, drained and packed open. There were intermittent flare-ups of signs of infection for which she received



Fig. 6. Case 10. A section of the colon showing acute necrotizing colitis.

antibiotics, including Achromycin orally, combined penicillin and streptomycin intramuscularly, and Chloromycetin intravenously. The course was rather stormy, and the patient received 11 transfusions. A culture of the abscess of the left hip on February 24, 1955, revealed Aerobacter aerogenes and beta hemolytic streptococcus. The A. aerogenes was totally insensitive to all antibiotics except neomycin, and only slightly sensitive to Terramycin. The streptococcus was totally insensitive. On March 20, 1955, the patient exhibited a period of shock which was successfully combated with intra-arterial blood under pressure and adrenal cortical extract. The patient showed some bloody, loose bowel movements, and the shock recurred on March 23, 1955, associated with abdominal pain, absent bowel sounds and abdominal tenderness. The nonprotein nitrogen of the blood was increased, hyponatrenia was present, and the blood count showed marked leukocytosis. Blood plasma was administered, but the patient went on to die in shock.

Autopsy Report: Death was attributed to acute necrotizing enterocolitis associated with the infected surgical wound following open reduction of the fracture of

the left femoral neck. The original infection was determined to be due to an insensitive Staphylococcus aureus. In addition, the autopsy revealed mild bilateral hydrothorax, pulmonary congestion, fatty changes in the liver, acute splenitis, chronic cholecystitis with a gall-stone, bilateral pyelitis, ureteritis cystica, and bilateral renal calculi. The lower ileum showed reddening of its mucous membrane and many grayish yellow necrotic patches. The changes were more severe in the colon. The background of the mucous membrane was gray-black, and the raised mucosal folds had a yellow-brown appearance. The areas of necrosis were covered by adhesive mucous. In the sigmoid and descending colon the necrotic areas were confluent. Microscopically, the section from the small bowel showed extensive inflammation and degenerative changes, with exudative fibrin and polymorphonuclear leukocytes forming on the mucosal surface of the bowel, particularly in areas where the glandular structure of the bowel was disrupted or necrotic. The exudate was present to a lesser degree over the intact area of the mucous membrane. The submucosa was much widened by edema, and a loose cellular infiltrate of predominantly mononuclear type was present. The muscularis, although somewhat edematous, was not much altered. The mucosal exudate contained many bacteria mixed in with the fibrin and mucus and desquamated cells. The bacterial composition appeared to be a mixture of cocci and bacilli. A culture of the bowel contents revealed A. aerogenes and unidentified cocci in culture.

Comment: In this instance a S. aureus wound infection was apparently successfully treated with some difficulty. Later, an aerobacter and a streptococcus appeared which were more difficult—or impossible—to eliminate. Many antibiotics were used, and finally a necrotizing enterocolitis resulted in which it was impossible to culture a resistant staphylococcus. Many additional pathologic lesions were discovered at autopsy, which probably contributed to death. Some authors have felt that acute necrotizing enterocolitis is directly related to or a type of pseudomembranous enterocolitis.

Case 11. This 53 year old male assembler was admitted to the hospital on May 1, 1955, with a history and clinical and x-ray findings of pneumonia of the right upper lobe. Sputum cultures revealed Diplococcus pneumoniae and Klebsiella pneumoniae. The patient had a history of moderately severe diabetes mellitus, and four years previously had received radiation therapy for lymphosarcoma, Subsequently, evidence was found which favored the possibility of lymphosarcomatous pulmonary infiltration as a predisposing factor. Combined penicillin and streptomycin therapy was started on admission. After bacteriologic studies were obtained the patient received Achromycin intravenously, and later orally, as well as sulfadiazine. Streptomycin was continued. On May 7 and 9, 1955, stool specimens failed to reveal any staphylococci. However, on May 10, 1955, two frothy loose bowel movements occurred, and the stool specimen showed a coagulase-positive, anhemolytic S. albus. Achromycin was immediately discontinued and erythromycin substituted. The patient was listless, tired and weak. The abdomen was moderately distended, but he had no severe drop in blood pressure. Intravenous electrolytes were administered, as well as aqueous adrenal cortical extract, tincture of opium and Wyamine sulfate, which within a matter of 24 hours controlled the enteritis and its associated symptoms. Erythromycin was continued until the fourteenth hospital day without further evidence of intestinal irritation. The patient eventually developed a large lung abscess.

Comment: Suspicion on the part of the attending physician resulted from the use of large dosages of antibiotics necessary over a period of time in a debilitated patient, and stool smears and cultures gave early definite warning. Erythromycin was apparently successful in inhibiting an overwhelming staphylococcic enteritis.

Case 12. This 45 year old sheet metal contractor was admitted to the hospital on May 15, 1955, because of signs and symptoms of acute appendicitis with peritonitis. At operation the diagnosis was confirmed, with the findings of an acute gangrenous ruptured appendix and generalized peritonitis. A culture of the peritoneal fluid revealed hemolytic Escherichia coli. Penicillin and streptomycin as well as Achromycin were used parenterally in therapy, and on May 17, 1955, the patient developed watery stools. On this date tetracycline was continued orally. Involuntary loose bowel movements continued. On May 20, 1955, nausea and vomiting with abdominal pain appeared. The patient was exhausted, began raising sputum and passed a pseudomembrane in the stool. Hiccups, confusion, cold, clammy skin, a weak, rapid pulse, thirst and abdominal distention ensued. A stool culture revealed S. aureus and E. coli, Diarrhea continued and the temperature became more elevated. Parenteral fluids containing electrolytes, blood transfusions, oxygen, ACTH, gastric suction and cortisone were vigorously employed in treatment. Erythromycin intravenously was substituted for tetracycline, and streptomycin was continued parenterally. By the following day a further fall in blood pressure to 88/60 mm, of Hg was recorded. and the patient remained confused and in a moribund state. ACTH and cortisone were continued, and Chloromycetin was administered intravenously. Another stool specimen revealed a hemolytic S. aureus. Continuation of rather vigorous treatment gradually led to improvement after two days, and by May 31, 1955, the patient was taken off antibiotics, Diarrhea had gradually stopped, fluid and electrolyte balance was restored, and the patient was able to take liquid foods.

Comment: This is another example of a staphylococcal enteritis which would probably have been fatal had the consultant not been alert and forced vigorous therapy. Diarrhea had been allowed to proceed for about 60 hours before specific diagnostic procedures and therapy were started. By this time profound effects of the enterotoxin on the fluid and electrolyte pattern of the body had been produced, requiring vigorous replacement measures as well as supportive therapy in the prevention of complete circulatory collapse. The importance of bacteriologic studies is apparent, as well as a high index of suspicion on the part of the attending physician.

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SUMMARIO IN INTERLINGUA

Inflammation intestinal con resultante formation de pseudomembrana es recognoscite depost plus que un seculo. Le recente augmento del incidentia de iste condition pare esser directemente relationate al administration de antibioticos. Le antibioticos a large spectros es implicate le plus communmente, sed etiam altere antibioticos—administrate sol o combinate—es responsabile. Le pseudomembrana resulta del action de varie irritantes, incluse ver venenos chimic, toxinas metabolic,

e productos bacterial. Il es probabile que factores mechanic, morbos associate, e le inherente resistentia del patiente es implicate. Iste serie complication occurre in conditiones chirurgic e non-chirurgic. Illo esseva notate longe annos ante le advento del antibioticos, sed il pare que le uso del antibioticos ha create un situation in que le riscos es augmentate.

Le variabilitate del resistentia bacterial contra le antibioticos resulta in un profunde alteration del equilibrio in le normal flora bacterial del varie cavitates del corpore, e specialmente del intestino. Quando le rivalitate del varie bacterios in le via intestinal dispare in consequentia del action antibiotic, un copiose superinfection

per un micro-organismo resistente pote resultar.

Es cognoscite que il occurre un rapide disveloppamento de resistentia al antibioticos del parte de staphylococcos, associate con le susceptibilitate al antibioticos del parte de multe altere bacterios intestinal. Iste adaptation o resistentia pare esser le consequentia del extense e probabilemente promiscue uso del antibioticos in nostre hospitales e communitates e ha resultate in un augmento del numero de portatores. Il es probabile que un foco de iste organismo in un area corporee altere que le vias gastrointestinal pote ager como fonte de implantation. Il existe indicationes que in le disveloppamento de superinfection intestinal per staphylococcos, enterotoxinas irritante produce inflammation pseudomembranose e etiam sever toxemia, statos de choc, e frequentemente disfallimento therapeutic e morte inexpectatemente subitanee.

Le thema es discutite super le base de un studio de 12 casos. Dece casos esseva confirmate autopticamente. In duo casos, le diagnose esseva establite ante morte, e le patientes esseva tractate con bon successo. Le characteristicas clinic es delineate, e suggestiones es facite in re prevention e therapia. Es sublineate le importantia de vigilantia e suspicion con respecto a iste risco in le uso del antibioticos.

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CONSTRICTIVE PERICARDITIS: A REVIEW AND LONG-TERM FOLLOW-UP OF 78 CASES *

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In 1935 White 1 reported a study of 15 cases of constrictive pericarditis. These, together with additional cases, have been the subject of later reports by Harrison and White 2 and Paul, Castleman and White.3 The last report, in 1948, comprised 53 cases. The present study includes: a long-term follow-up of the 26 patients living at the time of the 1948 report; 25 additional cases seen through 1954, and a review of the entire 78 cases, 65 of whom were operated upon. Two cases seen at this hospital in the latter period have not been included because of their short hospitalization period.

The purpose of this report is to: (a) reëmphasize the symptoms and signs characteristic of this disease; (b) review the usefulness of the electrocardiogram in these patients; (c) discuss the rôle of cardiac catheterization; (d) give the long-term postoperative results and contrast the course of the operated and the nonoperated cases.

CLINICAL DATA: SEX AND AGE

Of the 78 patients in the series there were 59 males and 19 females. This is a ratio of slightly greater than three males to one female. youngest age of apparent onset was two years and the oldest was 78. Of the 25 cases seen since 1948, the age at onset of symptoms was greater than 40 in half of the cases. This is in contrast to the initial 53 cases, in whom three quarters of the cases were less than 40 years old at the onset of symptoms. A figure giving age at time of operation and the results in the various age groups appears below (figure 1). Seventy-six of the patients were white, two were Negroes.

SIGNS AND SYMPTOMS

Dyspnea on exertion, ankle edema and abdominal swelling, in that order, are the most frequent complaints at the onset and as the disease progresses. Among the physical findings, hepatomegaly and neck vein distention

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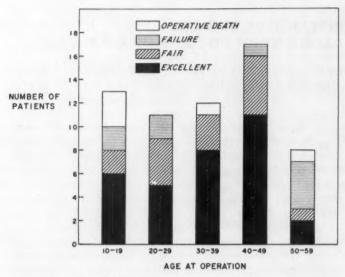


Fig. 1. Results of first operation in various age groups. (Two patients whose first operations were performed in other hospitals have been excluded.)

remain the most common. Deterling and Humphreys 4 have recently compared physical findings in this disease from seven series of cases. The incidence of various physical findings was essentially the same in the different series. In our series hepatomegaly was found in 89% of the cases, neck vein distention in 86%. Pleural effusion was present in 50% of our cases, ascites in 47%. Of the 25 patients seen since 1948, a definite mention of paradoxical pulse was made in 15 cases; it was considered positive in 11 and absent in four. Review of the records does not allow a definitive statement regarding the frequency of a third heart sound, but where specific mention was made it was a frequent finding. A review of the blood pressure showed that only one patient had mild hypertension preoperatively. (The highest blood pressure recorded in this patient was 160/100 mm. of Hg.) Aside from this patient, the highest systolic pressure found preoperatively was 130 mm. of Hg.

A review of the preoperative pulse pressures in all cases revealed:

Less than 20 mm. Hg	5 cases
20-29 mm. Hg	24 cases
30-39 mm. Hg	21 cases
40-49 mm. Hg	21 cases
50-59 mm. Hg	4 cases
More than 60 mm. Hg	3 cases

Postoperatively, elevation of the systolic pressure and widening of the pulse pressure were common findings. Ten of the 27 patients examined postoperatively had systolic pressures over 130, and five had systolic pressures of 160 mm. or over.

X-ray studies were done on all patients. The heart size was normal in 46.6%, slightly enlarged in 16.5%, and moderately to markedly enlarged in 36.9%. Calcium was found in the pericardium at x-ray, at operation or at postmortem examination in 60% of the cases. Of those cases in whom calcium was found in the pericardium, the calcium was visible by x-ray in 90%. Of the 58 patients who were fluoroscoped, cardiac pulsations were decreased or absent in 79%. However, it is well to note that pulsations were considered normal in 21% even after the fluoroscopist had been requested specifically to note cardiac pulsation.

ELECTROCARDIOGRAMS

The electrocardiograms were analyzed according to the rhythm, P waves, QRS voltage, QRS axis and T wave configuration. Electrocardiograms were available in 77 of the 78 patients. All 77 patients had electrocardiographic abnormalities.

Rhythm

Normal sinus rhythm throughout	44
Normal sinus rhythm with transient atrial arrhythmias	5
Normal sinus rhythm later changing to atrial fibrillation	6
Atrial flutter throughout	1
Atrial flutter changing to atrial fibrillation	2
Atrial fibrillation throughout	10

Forty-nine patients (64%) showed normal sinus rhythm (although five of these had transient atrial fibrillation or flutter). Twenty-eight patients (36%) had persistent arrhythmia, predominantly atrial fibrillation. The average age of patients with normal sinus rhythm was less than the average age of those with atrial fibrillation but of the 19 patients with persistent atrial fibrillation three were less than 20 years old. None of the 13 patients with atrial fibrillation prior to operation changed rhythm postoperatively. One patient with persistent atrial flutter preoperatively reverted to sinus rhythm postoperatively. Two patients postoperatively changed from atrial flutter to atrial fibrillation.

P WAVES

P waves of 0.12 second or longer in duration were considered wide. Those with definite double peaking (with peaks 0.04 second apart) were termed notched. Although the P waves appeared prominent, particularly in the presence of low QRS voltage and lowered T waves, only one patient had P waves greater in amplitude than 2.5 mm. (This patient died preoperatively. At autopsy no additional cardiac lesion was found to account for the large P waves.)

Of the 55 patients who showed normal sinus rhythm during some phase

of their disease, 54 tracings were available for measurement of the P waves. The P waves were:

Normal	15
Wide only	17
Wide and notched	20
Notched only	2

The 72% incidence of P wave abnormality is striking. It is interesting that many patients had the so-called P mitrale. There was little tendency for the P wave to change following surgery. In the 30 cases observed preoperatively and postoperatively, 20 remained essentially unchanged, five showed greater abnormality and five less abnormality.

QRS VOLTAGE

Forty-two (55%) of the 77 patients had low QRS voltage (amplitude of less than 5 mm. in all three standard limb leads).

ELECTRICAL AXIS

The electrical axis was determined in the frontal plane. In 71 patients the electrical axis of QRS was:

Between	+90 a	nd +	100	degrees	in	34
Between	+60 ai	nd +	90	degrees	in	20
Between	+30 ai	nd +	60	degrees	in	1
Between	+ 0 an	nd +	30	degrees	in	12
Indeterm	inate in	14		-		

Of the tracings with a determinate axis, 50.7% showed right axis deviation. There was no tracing with an axis to the left of zero degrees.

T WAVES

The T waves were abnormal in all 77 tracings. The abnormalities consisted of flattening or inversion.

In the 25 patients added to the series since 1948, precordial leads were taken routinely. Of these, 21 showed inverted or diphasic T waves in the left precordial leads. The remaining four showed an abnormal degree of flattening in the left chest leads. The right precordial leads showed no consistent pattern.

These figures reëmphasize the frequency of electrocardiographic abnormalities in constrictive pericarditis. No patient had a normal electrocardiogram. The following abnormalities were found (in order of their frequency):

T wave abnormality	100%
P wave abnormality	71%
ORS low voltage	55%
Right axis deviation	50%
Persistent atrial arrhythmia	36%

The majority of cases showed no changes in the electrocardiogram postoperatively. The changes encountered in the other cases varied. One postoperative tracing showed an absence of R waves across the entire precordium. In view of the removal of considerable epicardial surface in some cases, it was thought that no precise interpretation could be made of these bizarre changes.

CARDIAC CATHETERIZATION

In 1952 Scannell, Myers and Friedlich ⁵ reported the preoperative and postoperative cardiac catheterization findings in five patients of this series to point out the large element of left-sided constriction in some of these cases. Their work confirmed the observation of White, Alexander, Churchill and Sweet ⁶ and Burwell, ⁷ and the experimental work of Isaacs et al. ⁸ To date Myers and Friedlich have done catheter studies on 17 patients of this series. In essence, the characteristic catheter findings are: (1) moderately low resting cardiac output; (2) elevated pulmonary capillary pressure; (3) a characteristic early diastolic dip and plateau pattern in the right ventricular pressure tracing; (4) elevated and relatively uniform pulmonary wedge, pulmonary artery diastolic, right ventricular end diastolic, right atrial and vena caval pressures.

OPERATIVE MORTALITY

This report is primarily concerned with those patients whose first operation was performed at this hospital and on whom we have preoperative and postoperative data. The data below are calculated on the basis of these cases. Two patients (R. C.; L. H.) had operations on their pericardium prior to being seen here and are not included in these statistics.

Patients	Operative Deaths	Percentage
61	7	11.4
Operations		
71	7	9.8

Of the seven patients who had repeated operations here, two died during the procedure. This is a 29% mortality, and compares with five deaths, or an 8% mortality, in the 61 patients having their first operation.

This increased mortality for second or third operations wurranted a closer look at the results of repeated operations. The data are summarized in table 1.

Five patients had one additional operation. One patient died during this procedure, and a second operation in another patient was a failure. The results were considered fair in two others, while one patient obtained excellent results.

Three patients had two additional operations. The first patient (P. C.) received an excellent result from the first operation. Ten years later he had

a recurrence of symptoms. A second operation resulted in only fair relief, and the patient died during the third procedure. The second patient (M. W.) had been improved for eight years following the second operation and then had a recurrence of symptoms. The third operation was again successful, and she is now much improved one year postoperatively from the third procedure. The third patient (R. P.) made an excellent recovery after two operative failures. He is well 14 years later.

Three patients are not included in the above chart, as two of them (R. C. and L. H.) had a pericardial operation prior to being seen here, and the third (S. F.) had a second operation elsewhere. A 34 year old man (R. C.) was operated on twice before coming to this hospital. His third operation gave excellent results. Now, however, 14 years later, he is again beginning to have symptoms of constriction.

TABLE 1

Patient	Age at 1st Op.	Result, 1st Op.	Interval (years)	Result, 2nd Op.	Interval (years)	Result, 3rd Op.	Interva (years)
L. A.	18	Failure	2/12	Fair	Died of TBC six mos. later	_	-
G. P.	43	Failure	2	Excellent	8	-	-
J. N.	17	Sl. imp.	1 2/12	Failure	Died 7 yrs. later of embolism	-	_
F. S.	18	Failure	2/12	Died on operating table	_	-	-
S. F.	42	Fair (T)*	4	Fair	6/12		-
P. C.	30	Excellent	10	Fair	1 6/12	Died on op. table	
M. W.	24	Failure	8/12	Fair	8	Excellent 2	
R. P.	21	Fair (T)*	1 8/12	Failure	6/12	Excellent 12	

^{* (}T) = temporary

A 47 year old man (L. H.) had a fair result from the first operation and an excellent result from the second operation, 10 months later. A 47 year old man (C. K.) had a fair result from his first operation here, and his second operation was also followed by only partial and temporary relief.

FOLLOW-UP DATA

Since an occasional patient develops signs of constriction postoperatively after a symptom-free period of months or years, the term "excellent result" seems preferable to "cure." For that reason all cases operated upon have been divided into three groups:

- 1. Excellent: able to return to normal physical activity without symptoms.
- Fair: definite improvement but still having complaints of moderate degree.
- 3. Failure: showed no improvement.

Table 2 presents the over-all operative results. Due to their subsequent course and longer follow-up period, four cases from the 1948 series are now given a different classification rating (see below).

PATIENTS SEEN PRIOR TO 1948

Of the 15 patients thought to have an excellent result in 1948, all are still living. One patient (R. C.), who was considered as an excellent result at that time, now has mild symptoms of constriction. These symptoms have responded to salt restriction and digitalis, and further operation is not considered necessary now. This patient has had three operations. The other 14 patients are still considered excellent results. Six of these patients represent a follow-up of over 20 years, while nine represent a follow-up of over 10 years. The six patients operated upon over 20 years ago are all

TABLE 2
Total Cases Operated Upon—63

	Cases Operated upon at M.G.H.	Excellent Result	Fair Result	Not Improved	Operative Death	Died of Complicating Diseases
Prior to 1948	41	17	9*	4	5	6
Since 1948	23	15	5.	1	2*	0
Total	64*	32	14	5	7	6

* One patient (P. C.) appears in both of these columns as he obtained a fair result from operation in 1938, only to have two subsequent operations in 1949 and 1950. He died during the third procedure,

completely symptom-free and living normal, active lives. All six of these patients were operated upon by Dr. E. D. Churchill, and represent the pioneer work in this country in this field of surgery. The first operation was performed in July, 1928. A brief resumé of their cases follows:

CASE REPORTS

Case 1. Mrs. C. S. O. At age six she had a two-month episode of dyspnea, hepatomegaly and ascites. She was then well until age 14, when hepatomegaly and ascites recurred. After four years of progressive symptoms she was operated upon at the age of 18. Now, 27 years later, she does all her own housework, has no limitation of activity, and feels perfectly well. She has had two children and one major operation without difficulty. Physical examination reveals very slight neck vein pulsation in the upright position and "one fingerbreadth" hepatomegaly.

Case 2. Mrs. L. F. first noted symptoms at the age of 28. Two years later, after edema had progressed to the sacrum and abdominal wall with a right hydrothorax, a pericardial resection was performed. Now, 22 years later, she has no limitation of activity, and physical examination is negative.

Case 3. Mr. C. A. F. began to be bothered by dyspnea on exertion at the age of 17. Two years later operation was performed, at which time he had massive leg and scrotal swelling and hepatomegaly. Now, 22 years later, he works on his feet six

to seven hours a day, skis, swims and plays golf. Physical examination is negative

except for slight neck vein distention at 45°.

Case 4. Mr. L. C. developed ascites at the age of 12. After three months of abdominal swelling, necessitating one abdominal tap, he entered the hospital. Pericardial resection was performed, at which time a calcified pericardium was found. Twenty-two years later he still has no symptoms of constriction. His liver is felt two to three fingerbreadths below the costal margin, but he has had a large alcoholic intake for a number of years.

Case 5. Mrs. B. K. H. developed ascites at the age of five and one-half years. Symptoms remained unchanged for six and one-half years, when pericardial resection was performed at the age of 12 years. There was a slow recovery to excellent health during the ensuing year. Now, 21 years later, she has no limitation of activity. The only positive physical finding is very slightly increased neck vein distention with

pulsation.

Case 6. Mrs. D. G. began to notice fatigue at the age of 10. Four months later she developed ascites. At the time of operation, eight months later, her liver edge was palpable 6 cm. below the costal margin, and 2 L. of ascitic fluid were removed. Now, 20 years later, she works 40 hours a week in a factory and is free of all complaints. She has neck vein distention at 30°, but physical examination is otherwise negative.

Ten additional patients were thought to have been improved by surgery. Two (G. P. and D. P.) of those 10 had died from other causes at the time of the 1948 report. Of the eight remaining patients, two are now considered to show excellent results (D. G. and E. M.). Two others (W. R. and E. F.) are still living but are having many symptoms despite intensive medical treatment. The seventh patient (M. W.) has had a third operation (eight years after the second), and has had a good result from this operation despite a complicating atrial septal defect demonstrated by cardiac catheterization. The remaining three patients have died (M. C. of miliary tuberculosis, A. J. of congestive failure, and P. C. on the operating table at the time of a third operation).

NONOPERATIVE RESULTS

One patient was living in 1948 who was not operated upon, and another patient could not be traced. The first patient (C. T.) was having such mild symptoms that operation was not thought practicable. He subsequently became worse, developed pleural effusion, ascites and ankle edema, and was operated upon elsewhere six years after having been seen here. The operation was successful and now, five years postoperatively, he is actively at work six days a week at the age of 68.

The other patient (A. B.) was lost to follow-up at the time of the previous report. He had been seen last in 1934, and was sent home on a medical régime, to return in six months. Operation was not considered immediately indicated. He moved to New York, where he died of empyema four years later. Operation was never performed, and he was still in congestive failure at the time of his terminal illness.

NEW CASES

Of the 25 new patients seen since 1948, 22 have been operated upon. Fifteen (68%) are living and show excellent results. Five (23%) cases showed moderate improvement. Operation on one patient was a failure, and the last patient died on the second postoperative day of multiple pulmonary emboli.

Two of the patients who showed moderate improvement have subsequently died. The first (L. H.), a man of 42, died suddenly three years later in another city. Autopsy was not performed. The other patient (R. C.), although definitely improved after his operation, continued to be markedly restricted and died at home. Limited autopsy revealed some remaining constriction over the left ventricle.

Evaluation of the patient (N. W.) whose operation was a failure, including preoperative and postoperative catheter data, indicated that an adequate pericardiectomy was performed, but that complicating pulmonary disease had increased. The presence both preoperatively and postoperatively of left bundle branch block by electrocardiogram may indicate an element of coronary heart disease also.

Three patients were not operated upon. The first of these (G. S.) is a classic case of constrictive pericarditis. He has consistently refused operation, despite the fact that he is a cardiac cripple. The other two patients were not diagnosed prior to death (see below).

FAILURE TO MAKE THE DIAGNOSIS

The autopsy files of the Massachusetts General Hospital reveal only two cases found to have constrictive pericarditis at postmortem examination that were undiagnosed. The first patient had been followed at this hospital intermittently for 16 months. The onset of his symptoms occurred first at the age of 78. X-ray films revealed a markedly enlarged heart without pericardial calcification, and the diagnosis was not entertained.

The second patient was a 42 year old draftsman who had been followed for five years, with metastatic parathyroid carcinoma involving the nodes, pleura, lungs, diaphragm, phrenic nerve and superior vena cava. He had received radiation therapy to his anterior mediastinum three years prior to the onset of his symptoms. For the last 18 months of his life he was bothered by dyspnea, orthopnea, ascites and ankle edema. Although a separate process involving his pericardium was considered on one occasion, that diagnosis was discarded for widespread carcinomatous infiltration plus superior vena caval syndrome.

Autopsy revealed a 10 by 12 by 7 cm. mass in the superior mediastinum surrounding all of the great vessels entering and leaving the heart and constricting the superior vena cava. How large a part the fibrous pericardium which was demonstrated had to play in his symptomatology is questionable,

Two other patients, not included in this series, were thought to have had constrictive pericarditis, but it was not found at autopsy. It is interesting that at autopsy one of these patients had scleroderma heart disease, while the other had diffuse myocardial fibrosis of unknown cause. Both had pulsating neck veins and hepatomegaly. One had pulsus paradoxus. Neither had a third heart sound. A label of restrictive myocarditis might be applied to these cases.

INFLUENCING FACTORS

The cases classified as "excellent results" and those classified as "fair results" were compared to discover any features which might influence the operative prognosis.

The only positive correlation was that 29 of the 32 patients in the "excellent result" group were in sinus rhythm preoperatively, while three had atrial fibrillation. Of the 13 patients classified as "fair results," only five were in sinus rhythm preoperatively, while eight had either atrial flutter or fibrillation as their basic rhythm. It is interesting that all six patients who have been followed for over 20 years and who are considered excellent results had normal rhythm preoperatively and at last examination in 1955.

Duration of symptoms, heart size and calcification of the pericardium were compared in the two groups and showed no significant differences. It was interesting that 19 of the 32 cases showing "excellent results" had cardiac enlargement, and six of the 13 showing only "fair results" had cardiac enlargement.

PHYSICAL FINDINGS IN THOSE PATIENTS WHO SHOW EXCELLENT RESULTS

We were able to examine 27 of the 42 patients still living. Our colleagues here and elsewhere have sent us their physical findings on nine more patients. The remaining six were found either by mail or by telephone. The data below were derived from 25 patients considered to show excellent results who were examined according to a printed check sheet made up prior to the start of the study. Since some of the patients who were considered to show "excellent results" had minimal physical findings, it seemed wise to tabulate those findings:

Table 3

Postoperative Physical Findings in "Excellent Result" Group

stoperative rhysical rhidings in Excellent	Result On	u
Third heart sound	40%	
Neck vein distention or pulsation	40%	
Hepatomegaly	28%*	
Ankle edema	12%	

^{*} Two patients (8%) included in this figure have had high alcoholic intakes for many years, and cirrhosis cannot be ruled out.

DISCUSSION

White, Alexander, Churchill and Sweet 6 in 1948 reported their experience with three of these cases, pointing out the occasional preponderance of left ventricular constriction, the importance of cardiac catheterization in making this diagnosis preoperatively, and the benefit from choosing a transthoracic approach to attack this problem.

In the first of their cases, autopsy revealed that the mitral valve was actually pressed upon externally on its lateral aspect by the calcified pericardium, "resulting in definite mitral stenosis." Recent work by several different investigators 5, 8, 9 has pointed to the importance of left ventricular denudation in these cases. From these studies one would expect that the earlier operative results, when the attack was not directed primarily at the left ventricle, would have been less successful than more recent ones. On a percentage basis this is true. However, the fact remains that there is a striking number of excellent results from the earlier cases which have now been followed for over 20 years and are still asymptomatic. It is probable that most of these did have at operation at least some clearing of their left ventricular constriction.

An intensive study was not made to elucidate further the etiology of this disease. Deterling and Humphreys have recently reviewed this subject. Some of our cases had a history compatible with acute pericarditis, rheumatic fever or penetrating chest wound. However, one fact stood out, and that was that when the etiology was unequivocal it was invariably tuberculous. The absence of active pulmonary tuberculosis was interesting. Inquiries at follow-up examinations revealed histories such as the following:

- 1. One patient in whom the cause was not established in the previous series died of miliary tuberculosis four years later.
- 2. Another patient in the "excellent result" group, the etiology undetermined in 1948, has had tuberculous adenitis for the last five years.
- 3. A patient in whom the cause has not been proved states that his daughter was admitted to a sanatorium for apical tuberculosis the year after his admission to this hospital.
- 4. Another patient now remembers that her sister had a nephrectomy for renal tuberculosis 25 years prior to the onset of the patient's disease.

An occasional patient has lived with mild symptoms of congestive failure in a compensated state for a number of years. However, all patients who were considered too ill for operation died shortly thereafter. Several of the patients whose symptoms were considered too mild to warrant operation subsequently had a progression of symptoms so that operation later became necessary.

A point regarding the age of onset should be mentioned. One patient did not develop symptoms until the age of 78. This illustrates the hazard

of easy acceptance of arteriosclerosis as the diagnosis of otherwise unexplained congestive failure in elderly patients.

That all 77 of the available electrocardiograms were abnormal seems important in a negative way. In a patient suspected of having constrictive pericarditis, a normal electrocardiogram is strong evidence against that diagnosis.

A normal or even increased pulse pressure does not rule out constrictive pericarditis. Four of the 78 patients had pulse pressure greater than 60 mm. Hg. Nine per cent of the patients had a pulse pressure greater than 50 mm. Hg.

In regard to operative mortality, it seems that, despite the higher risk of a second or third operation, there were enough striking improvements to warrant it when necessary. From the 11 patients in this series who had repeated operations it was not apparent that the success or failure of the previous operation had any direct bearing on the outcome. A detailed operative note of the previous pericardial resection would be of great value in deciding if another operation would be of any benefit. The amount of pericardium previously resected, the degree of adherence of the pericardium to the epicardium, and the status of the myocardium per se would all be determining factors in deciding upon later operations.

In a patient who has had a previous pericardiectomy, the onset of congestive failure may be the result of persistent or further pericardial constriction or of myocardial failure per se. Likewise, there are patients with valvular or other types of heart disease in whom an element of pericardial constriction is suspected. In these cases, abnormal neck vein pulsation and hepatomegaly plus pulsus paradoxus and a third heart sound would be strong evidence in favor of an element of constriction. Where the diagnosis remains in doubt, cardiac catheterization may help by demonstrating a characteristic early diastolic dip and plateau in the right ventricular pressure tracing, together with equal filling pressures of left and right ventricles (wedge pressure approximately equal to left ventricular end diastolic pressure).

It seems worth while to emphasize the occasional very bizarre postoperative electrocardiographic patterns of these patients, some of whom were operated upon as many as 10 years previously.

Three patients had excellent results for many years, only to have a recurrence of symptoms. Two of these patients have subsequently come to further operation. Extensive calcification over the posterior pericardium was found in both cases, but the exact cause of the recurrence of symptoms after a period of so many symptom-free years was not explained. This could be due to right ventricular failure secondary to long-continued pulmonary hypertension.

SUMMARY

1. The clinical aspects of 78 cases of constrictive pericarditis have been studied. Forty-two patients who have been operated upon are still living. Six have been followed for over 20 years, 10 for over 10 years, and 11 for over five years. All of the patients followed over 20 years are living normal, unrestricted lives.

2. Operative results have been classified and operative mortality has been calculated on initial and later operations. The majority of patients who are symptom-free postoperatively show some abnormal physical signs. The clinical features of the patients classified as showing excellent results, fair results and failures have been compared.

3. Several interesting features have been noted:

(a) Dyspnea, ankle edema and abdominal swelling are the most frequent complaints. Neck vein distention and hepatomegaly were the most frequent physical findings.

(b) A systolic blood pressure above 130 mm. Hg was found in only one patient preoperatively, whereas wide pulse pressures were not rare (greater than 50 mm. Hg in 9% of cases). Systolic blood pressures commonly rose postoperatively, but no patient became seriously hypertensive.

(c) Cardiac enlargement was present in one-half the cases. Cardiac pulsations were diminished in four fifths of the cases but were fluoroscopically normal in the other fifth.

(d) Abnormal electrocardiograms were present in every case. The T waves were abnormal in 100% of the cases. The P waves were abnormal in 72% of those cases with normal rhythm. Atrial arrhythmias were common, having been found in 34 of the 78 cases; fibrillation was identified in 27, being constant in 19, while flutter occurred in three, two of which changed to fibrillation.

(e) Calcification was noted in the pericardium in 60% of the cases.

4. The characteristic cardiac catheter findings have been reviewed.

SUMMARIO IN INTERLINGUA

Iste articulo representa le quarte reporto ab le clinica del Hospital General Massachusetts in re un considerabile serie de casos de chronic pericarditis constrictive, colligite in le curso del annos. Le prime tres reportos esseva publicate in 1935, 1942, e 1948.

Al tempore presente, le serie total consiste de 78 casos. Sexanta-tres esseva operate. Quaranta-duo de iste 63 patientes vive ancora. Sex esseva sub observation consecutori durante plus que 20 annos. Illes es perfectemente ben e vive vitas normal. Un medietate del casos operate, i.e. 32 ex 63, obteneva resultatos excellente. In 14, le resultatos esseva satis bon. Cinque casos monstrava nulle melioration. Sex patientes moriva ab complicationes. Il habeva septe mortes operatori.

Le signos signalante le presentia de iste morbo in le presente serie de patientes esseva inflation abdominal, distension del venas del collo, e un minus pronunciate grado de edema del talo. Dyspnea esseva un symptoma commun. In le electrocardiogramma, anormal undas T esseva notate in omne casos. In un numero de casos, le electrocardiogramma se meliorava post le operation sin retornar integremente al stato normal.

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INFILTRATIVE EOSINOPHILIA * †

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LOEFFLER's original description of the syndrome that bears his name 1, 2 has been followed by numerous publications. Modalities and gradients of apparently the same syndrome, differing mainly in the extent and duration of the pulmonary infiltrations and the persistence of clinical manifestations, have been subjects for extensive speculation. These have been complicated by the numerous names and eponyms that have appeared in the literature, among others: tropical eosinophilia,8 acute febrile eosinophilic asthma,4 eosinophilic infiltration of the lungs,5 familial eosinophilia,6 eosinophilic asthma,7 Weingarten's syndrome,8 pseudotuberculosis of the lungs,9 benign eosinophil leukemia (Treu),10 pulmonary acariasis,11 eosinophilic lung,12 pulmonary eosinophiliosis, 18 eosinophilia with splenomegaly, 14 eosinophilic pneumopathy, 18 grande eosinophilié sanguinaire, 16 and pulmonary infiltration with eosinophilia (P. I. E. syndrome). The numerous etiologic factors postulated have led to further confusion in the elucidation of the pathogenesis of this condition. 18-40

For the sake of better clinical understanding, an attempt was recently made to group all these phases, gradients and/or variants of hypersensitivity characterized by inflammatory alterations with profuse eosinophilic infiltration in various organs and a circulating hypereosinophilia under the term, infiltrative eosinophilia.41 There is enough clinical evidence to suggest that, from the therapeutic point of view, there is a group of variants, gradients or phases of this hypersensitivity state that responds favorably to arsenicals, and another that remains unaffected.

In this communication we will be concerned mainly with the analysis of the data obtained from 33 cases belonging to the arsenic-sensitive group studied for periods ranging from one to six years.

ANALYSIS OF CASES

Of the 33 cases, 29 were permanent residents of San Juan or vicinity. three acquired the disease in New York City, and one in the Dominican Those taken with the disease in the Temperate Zone had lived Republic.

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in New York for several years and, on recommendation of their physicians in the mainland, returned to Puerto Rico seeking relief from severe asthmatic manifestations. This would indicate that the disease is not exclusively tropical, and would invalidate the significance of the term "tropical eosinophilia," since none of these patients suffered from pulmonary manifestations with hypereosinophilia prior to emigration to the continental United States.

Twenty-one were males and 12 females: 16 were under 40: the youngest was 12, the oldest 70, with an average age of 38 years; 31 were white. Although the sample is too limited to warrant definite conclusions, it appears that the disease may occur at all ages, is slightly predominant in the male,

and is seen almost exclusively in the white race.

There was no evidence to suggest a causative relationship with work. since all females were housewives and the males were engaged in different trades: carpenters, clerks, merchants, students, messengers, janitors and watchmen. (Four were pensioned employees with no particular work or

hobby.) All were considered as indigents.

Twenty-nine patients were admitted to the hospital with complaints referable to the underlying illness: severe asthma in 21; dry cough with moderately severe asthmatic manifestations in two; and generalized lymphadenopathy, severe epigastric distress, weakness, nasal discharge, chills, fever and diarrhea in six. Four were found to suffer from the condition on routine blood studies though they had been admitted for unassociated illnesses: an inguinal hernia, a subarachnoid hemorrhage, jaundice and a uterine prolapse. However, a history of asthma of variable intensity and duration was obtained in each instance.

The onset was insidious in 30 and acute in three. Generally, the disease was ushered in by gradual appearance of general malaise and weakness, with a sensation of tightness of the chest and, eventually, a wheezing respiration. Exacerbations of the asthmatic manifestations, accompanied by fever of

from one to 14 days' duration, were frequently observed.

Asthma was present in 28 instances: severe in 11, moderate in seven and mild in 10. The asthmatic manifestations had persisted for less than six months in 16, and for from six months to 38 years in 12. Of the latter group with a protracted course, six had concomitant spasmodic (allergic) bronchial asthma with persistence of symptoms after arsenical therapy and after the hemogram and myelogram had reached normality. However, in one instance of unusual duration of uncomplicated asthma (20 years), all symptoms subsided after therapy in concomitance with a reduction of the eosinophils in the peripheral blood and bone marrow. In one instance, spasmodic bronchial asthma apparently appeared simultaneously with the infiltrative eosinophilia. Therapy was followed by relief of the eosinophilic infiltrations, while the pulmonary symptomatology remained unaltered.

Paroxysmal, hacking, scarcely productive cough was perhaps the most dominant manifestation in 30 instances. It was most prominent during the late afternoon and evening. It frequently preceded the exacerbations of asthma, and at times induced vomiting. The sputum was frequently loaded with eosinophils.

Fever was present in 22 instances. It was over 102° F. in 17. The highest levels appeared during the asthmatic exacerbations, which lasted for from three to 12 days, followed by irregular, low grade, intermittent spikes of several days' duration which subsided spontaneously. The fever curves were generally irregular, and some of the patients were unaware of the increased temperatures.

A history of one or more allergic phenomena was obtained in 26 instances: allergic rhinitis in 15, spasmodic bronchial asthma in six, urticaria in two, penicillin sensitivity in two, and contact dermatitis in one. Of the four submitted to skin tests, three showed sensitivity to house dust and one to a mixed respiratory vaccine.

Of the three patients suffering from sinusitis, two had spasmodic bronchial asthma. The third had suffered for many years from maxillary sinusitis, which had required frequent drainages, before developing asthma and eosinophilia. The asthmatic manifestations and eosinophilia disappeared promptly after arsenical therapy, despite the persistence of the sinusitis.

Persistent hypertension was observed in two instances. This was attributed to acute glomerulonephritis in one, and to chronic glomerulonephritis of five years' duration in the other. Mild, transitory hypertension during severe exacerbations was observed in seven cases.

The constant generalized weakness and lassitude reduced the patient's working efficiency. Moderate weight loss was recorded in 18, anorexia in 17, and gastrointestinal disturbances (nausea, vomiting and diarrhea) in 10. Arthralgia without evident joint alterations, and generally accompanied by other allergic manifestations, was recorded in four instances.

Nontender splenomegaly was present in five cases; the organ was firm in three and soft in two. Generalized, discrete and rubbery lymphadenopathy was noted in 12 instances. In one the marked, generalized lymph node enlargement served as the presenting complaint. Enlarged tonsils were encountered in four, conjunctivitis in two, and subcutaneous nodules in the bony prominences of the arms in another.

Nontender, moderate hepatomegaly was recorded in seven cases, presumably due to hepatic cirrhosis in two instances. In one case, serial liver biopsies showed periportal eosinophilic infiltration with granuloma formation, and progressive fibrosis after arsenical therapy.⁴¹ It must be emphasized that corticotropin failed to affect the hepatic pathologic alterations (table 1).

Eosinophilic leukocytosis, varying from 2,000 to 67,250 per cubic millimeter of blood, and as high as 97% of the total white cell count, was the most characteristic and constant laboratory finding. The eosinophils were ma-

ture, with only occasional hyperlobulations, and, in many instances, variable in number at different hours and days. The actual neutrophil, lymphocyte and monocyte counts were generally within normal limits, although the percentage appeared lower in the differential series. Aside from an instance of mild microcytic hypochromic anemia associated with uncinariasis, and another of nutritional macrocytic hyperchromic (megaloblastic) anemia, the hemoglobin and red cell values were normal. The eosinophilic levels remained unaltered after the administration of corticotropin for the Thorn test.

The bone marrow showed moderate to marked increases in the eosinophilic elements, varying from 17 to 60%. The increases were dominated by the mature and stab eosinophils, with only moderate increases in eosinophilic metamyelocytes and but slight preponderance of myelocytes. This

Table 1
Clinical Findings in 33 Cases of Infiltrative Eosinophilia

Cough	30	Tightness of chest	10
Dyspnea	28	Chest pain	7
Wheezing	28	Hepatomegaly	7
Expectoration	23	Hypertension	7
Fever	22	Splenomegaly	5
Weight loss	18	Arthralgia	4
Anorexia	17	Dizziness	4
Rhinitis	15	Tonsillitis	4
Headache	15	Chills	3
Weakness	12	Sinusitis	3
Lymphadenopathy	12	Urticaria	2
General malaise	11	Conjunctivitis	2
Pharyngitis	11	Penicillin sensitivity	2
Nausea and vomiting	10	Contact dermatitis	1
Diarrhea .	10	Subcutaneous nodules	1

was mainly a quantitative alteration, which was never mistaken for eosinophilic leukemia. Neither inclusion bodies nor abnormal premature cells were observed, and, aside from the two cases cited above, the erythrocyte series were within normal limits.

All but one case showed hastened erythrocyte sedimentation rates. Hyperglobulinemia of 3.1 to 5.2 gm. per 100 c.c. of blood was found in 11 of 12 cases tested. The serum albumin was quantitatively within normal limits. Electrophoretic studies in six instances invariably showed definite increases in the gamma fraction. The cephalin flocculation test was doubtful in four and positive in one, while the thymol turbidity was negative in six. The Bromsulphalein test showed abnormal retention by the two patients suspected of hepatic cirrhosis, and was normal in four other instances.

Roentgenologic studies of the lungs were abnormal in 25 and within normal limits in eight cases. The abnormal pulmonary findings were of five main types: (1) increased bronchovascular markings; (2) miliary infiltrates persisting for months; (3) transitory patchy infiltrates; (4) diffuse, miliary, nodular and fibrotic infiltrates following therapy, and (5) a combination of these findings. The radiologic alterations will be the subject for a separate communication.

The almost invariably whitish, viscid sputum frequently contained numerous eosinophils, mostly mature but occasionally mononuclear. Bronchoscopic studies in one instance revealed generalized edema and erythema of the bronchial mucosa with a mucus plug in the right main bronchus. Culture of the aspirated mucus failed to grow pathogenic bacteria.

Serial stool examinations revealed Trichuris trichiura in 11; T. trichiura and Necator americanus in five; T. trichiura and Ascaris lumbricoides in one; A. lumbricoides in one, and N. americanus in two. Repeated stool examinations and rectal biopsies failed to show ova of Schistosoma mansoni in all but one, and blood studies for microfilariae and malaria were invariably un-

TABLE 2

Laboratory Findings in 33 Cases of Infiltrative Eosinophilia

Tests	Number of Cases	Number Abnormal
Eosinophil count	33	33
Bone marrow eosinophils	33	33
Gamma globulins	6	6
Cutaneous sensitivity	4	4
Sedimentation rate	33	32
Serum globulins	12	11
Lung x-rays	33	25
Albumin (urine)	33	17
Eosinophils in sputum	14	8
Serologic test for syphilis	33	10
Bromsulphalein retention	6 5 33	2
Cephalin flocculation test	5	1
Erythocyte count and hemoglobin		2
Cold hemagglutinin titers	16	0
Heterophil antibodies	16	0
Thymol turbidity	6	0
Nonprotein nitrogen (blood)	7	0
Eosinophils in urine	4	0
Eosinophils in spinal fluid	4	0
Phenolsulfonphthalein test	4	0
Urea clearance test	4	0
Electrocardiograms	4 4 3	1
Eosinophils in vaginal discharge	3	0
Biopsy specimens (lymph nodes)	2	2
Biopsy specimens (appendix)	1	1

rewarding. Effective antihelminthic therapy in four cases infected with N. americanus and in one infected with A. lumbricoides failed to alter the eosinophilic leukocytosis or the clinical symptomatology within an average of 40 days. In all those receiving arsenical therapy in the presence of intestinal parasitism, prompt and favorable clinical responses were recorded.

The serologic tests for syphilis were positive in three, doubtful in seven and negative in 23. Among the positive reactors with a definite history of syphilis, titers ranged from 2 to 80 units. The doubtful reverted to normal after oral or intravenous arsenicals. Heterophil antibody and cold hemagglutinins were absent in the 16 cases tested, and the Widal, Weil-Felix and brucella agglutinations, tested in four instances, were negative.

No eosinophils were found in the urinary sediment (four cases), spinal fluid (four cases), or vaginal secretions (three cases). The nonprotein and

urea nitrogen as well as the phenolsulfonphthalein and urea clearance tests were normal in the four patients tested. Electrocardiographic studies failed to reveal alterations in three, while in one there was persistent right axis shift, and transitory ST and T wave depression in Leads 1 and 2 as well as in V_1 , V_2 and V_3 during the asthmatic exacerbations.

Lymph node biopsy specimens demonstrated a diffuse hyperplasia with eosinophilic infiltration in two instances. Serial sections of the appendix in one instance showed moderate eosinophilic infiltration without vascular changes, suggesting a collagen disorder (table 2).

Although treatment with intravenous oxophenarsine (Mapharsen) and oral Carbarsone and Fowler's solution was invariably effective in the correction of the peripheral and bone marrow eosinophilia, seven patients with concomitant spasmodic bronchial asthma failed to attain a favorable clinical response in spite of the complete elimination of the typical pulmonary infiltrates. It must be emphasized that correction of the hastened erythrocyte sedimentation rates and hyperglobulinemia followed or accompanied the return of the myelogram to normal. The prompt and permanent reduction in the gamma globulins which followed the administration of arsenicals was not observed with corticotropin and cortisone therapy.

As has been emphasized elsewhere, and confirmed by our present studies, while the continuous administration of corticotropin led to a rapid dissolution of the circulating and infiltrating eosinophils, it failed to alter the bone marrow picture either qualitatively or quantitatively. However, with arsenical therapy there was a rapid dissolution of the circulating and infiltrating eosinophils concomitant with a marked depression of the production of the eosinophils by the bone marrow.⁴¹

CASE REPORTS

Case 1. A 48 year old white merchant from the Dominican Republic was admitted to the San Juan City Hospital on January 24, 1950, complaining of occasional mild and transitory attacks of asthma for the last seven months. Physical examination revealed scattered râles, rhonchi and wheezes throughout both lung fields.

On admission the red cell and hemoglobin values were normal and the white cell count was 32,200 per cubic millimeter, with 75% eosinophils, 10% neutrophils and 15% lymphocytes. The stools showed ova of *T. trichiura*; the blood Kahn and Wassermann reactions were strongly positive, while the spinal fluid serology, the heterophil antibodies and cold hemagglutinins were negative. The total serum proteins were 8.62 gm.%, of which 4.34 gm.% were globulins. The sputum was repeatedly negative for *Mycobacterium tuberculosis*, and the urinalyses were normal. The bone marrow showed increased eosinophilic elements (46.5%), with 1% eosinophilic myelocytes, 2.5% metamyelocytes, 3% stabs and 40% mature eosinophils. Roentgenologic studies showed bilateral mottled infiltrations of the lung parenchyma simulating either miliary tuberculosis or Boeck's sarcoid.

The daily oral doses of 2 gm. of Aureomycin (500 mg. every six hours) for 10 days (February 1 to 10) failed to affect the eosinophilic levels. On February 27 the patient was given intravenous typhoid vaccine (initial dose, 5 million bacilli), followed by two doses of 7.5 millions at weekly intervals. Each injection was fol-

lowed by a 48-hour rise in temperature (to 102.5° F.), with transitory but marked reduction in the circulating eosinophils. However, the pulmonary symptomatology remained unchanged (chart 1). Six weekly intravenous injections of 40 mg. of oxophenarsine (Mapharsen), started on April 6, led to a gradual decrease in eosinophils. This was accompanied by a rapid clinical improvement, a radical attenuation of the qualitative serologic tests for syphilis, a noticeable reduction in the total proteins, and a marked decrease in the serum globulins.

A two year follow-up demonstrated complete clinical recovery, aside from mild pulmonary emphysema. The serum proteins and eosinophil elements in the peripheral blood and bone marrow were within normal limits, and the serologic tests for syphilis were negative.

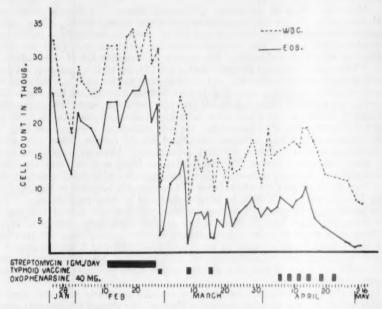


CHART 1. Depicting changes in the total leukocyte and eosinophil counts following intravenous injections of typhoid vaccine and oxophenarsine (Mapharsen) in case 1.

Case 2. A 54 year old white Puerto Rican male had had hay fever since 1925, and frequent attacks of spasmodic bronchial asthma since 1935. He had had several hospitalizations elsewhere for status asthmaticus since 1949.

On February 27, 1950, he was forced to visit his physician because of a persistent watery nasal discharge and a bothersome, persistent sneezing. His chest x-rays were normal, and the white cell count was 16,100 per cubic millimeter, with 85% neutrophils and 15% lymphocytes. Intracutaneous tests showed hypersensitivity to house dust and a stock respiratory vaccine. Following the subcutaneous injection of 0.1 c.c. of the latter on February 28 he developed a violent attack of asthma, requiring immediate hospitalization. At this time his white cell count was 9,850 per cubic millimeter, with 59% neutrophils, 26% lymphocytes and 15% eosinophils. He responded poorly to parenteral aminophylline and adrenalin, but after several intra-

venous injections of typhoid vaccine he showed rapid clinical improvement and was discharged asymptomatic on March 9.

The patient was hospitalized elsewhere on March 16 in status asthmaticus. The x-rays showed diffuse, fluffy infiltrations of the pulmonary parenchyma, and leukocyte counts of 9,600 to 12,600 per cubic millimeter, with 41 to 47% eosinophils. The stools revealed ova of *T. trichiura*, and the urinalyses and blood serologic tests for syphilis were negative.

On March 21 the patient was started on 40 mg. of oxophenarsine (Mapharsen) intravenously at three day intervals. The drug was discontinued after the fourth injection because of severe nausea and vomiting and watery diarrhea. He was referred to us on April 13, 1950, after three days of therapy with 0.25 gm. of Carbarsone twice daily.*

Aside from moderate pulmonary emphysema, wheezes and rhonchi throughout both lung fields, the physical examination was within normal limits. X-ray studies revealed increased vascular markings and diffuse, fluffy parenchymatous infiltrations throughout both lungs. The leukocyte count on admission was 9,950 per cubic millimeter, with 55% eosinophils. The sputum was negative for M. tuberculosis.

While under Carbarsone therapy (until April 18), the patient frequently required sedatives, and parenteral adrenalin and aminophylline for the transitory relief of the severe asthmatic symptoms, until May 1, when definite improvement was noted. On April 27 his leukocyte count was 24,500 per cubic millimeter, with 34% eosinophils; on May 3, 16,250 per cubic millimeter, with 25% eosinophils; on May 8, 8,000 per cubic millimeter, with 2% eosinophils. He was discharged improved on May 10. The pulmonary infiltrates remained unchanged for 18 months, when only small, scattered scars were visible in the lung parenchyma. Although hospitalized twice for status asthmaticus during 1953, the patient has failed to show either significant eosinophilia or radiologic pulmonary alterations suggestive of infiltrative eosinophilia.

Case 3. A 64 year old white Puerto Rican male was admitted to the San Juan City Hospital on July 19, 1951, in status asthmaticus of three days' duration. This was accompanied by nausea, vomiting, anorexia and a weight loss of five pounds. He stated that since May 7, 1951, he had suffered from daily episodes of severe asthma, much worse at night, and resistant to the usual medications. He attributed his illness to an emotional upset on the day of onset. He had a bizarre, recurring, severe abdominal pain requiring repeated and prolonged hospitalizations in 1946. The white cell count at that time did not exceed 8,550 per cubic millimeter, with normal differential values.

The physical examination on admission revealed an elderly man with signs of recent weight loss and in acute respiratory distress. He showed a moderately severe emphysema, with wheezes, rhonchi and râles heard throughout both lung fields. The liver was moderately enlarged but not tender.

The red cell and hemogloblin values were within normal limits. The leukocyte count ranged from 12,500 to 28,000 per cubic millimeter, and the actual eosinophil counts from 9,000 to 24,000 per cubic millimeter. The sedimentation rate varied from 26 to 36 mm. per hour; the total serum proteins were 8.06 gm.%, with 3.75 gm.% of globulins; the cephalin-cholesterol flocculation test was 2 plus in 48 hours, and the icterus index was graded four. The blood nonprotein nitrogen and the urea clearance and phenolsulfonphthalein tests were within normal limits. The urinalyses and serologic tests for syphilis were negative. No S. mansoni ova were demonstrated in the stools or rectal biopsy, and the blood smears failed to show microfilariae or malarial parasites. Repeated stool examinations showed ova of T. trichiura. The cold hemagglutinin and heterophil antibodies were absent. The tuberculin test was

^{*}We thank Dr. Angel Marchand, consultant in allergy, San Juan City Hospital, for the referral of this patient.

positive, but no M. tuberculosis organisms were seen in the sputum and gastric washings. The sputum was loaded with eosinophils, and the bone marrow was heavily infiltrated with eosinophilic elements (56.5%): 2.5% myelocytes, 2% metamyelocytes and 51.5% mature eosinophils. The chest x-rays were within normal limits.

The oral administration of 0.25 gm. of Carbarsone twice daily from August 20 to August 31 led to an early, transitory rise in the circulating eosinophils, followed

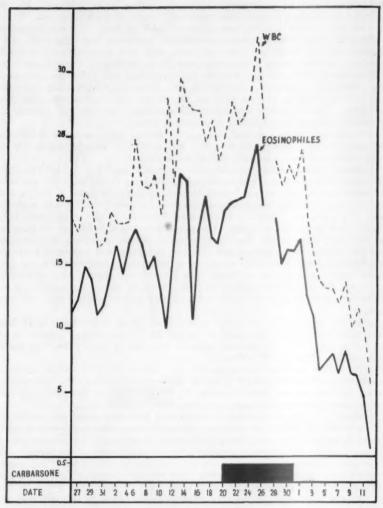


CHART 2. Illustrating the changes in the total white cell and eosinophil counts before and after the oral administration of 0.25 gm. of Carbarsone twice daily for 11 days (case 3).

by a slow but progressive dissolution of these cells (chart 2). The asthmatic symptoms had permanently disappeared by August 30. The eosinophil count was 6,950 per cubic millimeter on August 30, when 28% of the bone marrow elements were eosinophils. By November 30 the patient was in good health and had had a weight gain of eight pounds, and the eosinophil count, sedimentation rate and bone marrow were normal. A three and one-half year follow-up showed complete recovery, aside

from slight pulmonary emphysema.

Case 4. A 37 year old white Puerto Rican housewife was admitted to the San Juan City Hospital with a history of bronchial asthma since childhood. In 1946 she had noted extremely severe recurrences of asthma at weekly intervals, lasting for from one to three days and usually accompanied by fever. An examination on February 27, 1950, revealed wheezes and rhonchi throughout both lung fields, and a leukocyte count of 10,950 per cubic millimeter, with 30% eosinophils. The attacks of asthma persisted during a pregnancy that led to delivery of a premature infant on December 23, 1950. At this time the leukocyte count was 13,050 per cubic millimeter, with 31% eosinophils. On April 6, 1951, it was 26,500 per cubic millimeter, with 76% eosinophils, and on May 11, 29,100 per cubic millimeter, with 59% eosinophils. The increasing severity of the asthmatic state and her physical deterioration prompted her admission on August 6, 1951.

Physical examination showed malnutrition, carious teeth, moderate emphysema, expiratory wheezes, rhonchi and râles over both lung fields, enlarged inguinal lymph

nodes, and chronic cervicitis with profuse leukorrhea.

Laboratory examinations revealed leukocyte counts ranging from 21,000 to 27,400 per cubic millimeter, and actual eosinophil counts from 11,500 to 17,700 per cubic millimeter; normal red cell and hemoglobin values; an icteric index of 10.7; a sedimentation rate of 52 mm. in one hour; total serum proteins of 6.25 gm.%, with 3.01 gm.% of globulins; a 2 plus cephalin-cholesterol flocculation test in 48 hours, and a normal blood nonprotein nitrogen. The stools were negative for ova or parasites, and the blood was negative for microfilariae or malaria parasites. The serologic tests for syphilis were negative, and cold hemagglutinins and heterophil antibodies were absent. Many eosinophils were seen in the sputum, none in the spinal fluid, vaginal discharge or urinary sediment. The bone marrow showed 2.5% eosinophilic myelocytes, 5% eosinophilic metamyelocytes, and 29.5% mature eosinophils. X-ray studies demonstrated extensive fluffy infiltration of both hilar areas and pulmonary bases.

Fowler's solution (1% potassium arsenite) was given in oral doses of 15 drops three times a day from August 12 to August 23. A progressive decrease in the circulating eosinophils followed soon after the initiation of therapy, reaching normal levels on November 30, 1951 (chart 3).

The patient remained asymptomatic until March 26, 1952, when attacks of asthma recurred, unaccompanied by either fever or eosinophilia. The bone marrow picture has been normal since December 15, 1951. However, the pulmonary infil-

trations are still evident, although less extensive.

Case 5. A 23 year old white Puerto Rican housewife stated that on May 1, 1951, she suddenly developed persistent nocturnal paroxysmal cough with a sensation of tightness in the chest lasting from one to three hours. Daily severe attacks of asthma during the evening, disappearing in the small hours of the morning, low grade fever, anorexia, occasional nausea and vomiting, easy fatigability, and gradual weight loss appeared in September, 1951. She was hospitalized on October 30, 1951, because of a severe status asthmaticus of three days' duration.

She was in severe respiratory distress, with a cold and moist skin, a temperature of 99.5° F.; pulse, 140; respirations, 36 per minute; blood pressure, 140/100 mm. of Hg. The conjunctivae and pharynx were injected, and she had severe emphysema,

with numerous wheezes, rhonchi and coarse râles. Her leukocyte count was 20,500 per cubic millimeter, with 90% neutrophils.

Bronchodilators (parenteral adrenalin and aminophylline) and sedatives were ineffective, as on previous occasions. Because of increasing respiratory embarrass-

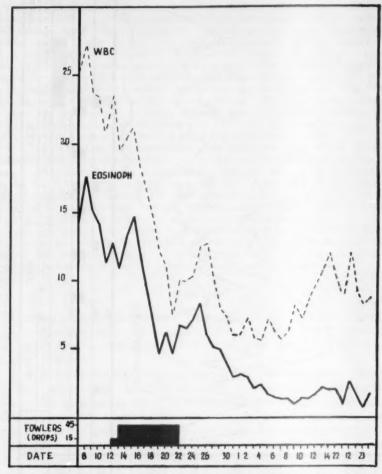


CHART 3. Illustrating the changes in the total white cell and eosinophil counts following the oral administration of Fowler's solution for 10 days (case 4).

ment, she was bronchoscoped eight hours after admission. There was extensive edema of the bronchial mucosa, and a large mucus plug was aspirated from the right main bronchus. Rapid improvement followed, and she was asymptomatic by November 6. However, at this time the white cell count was 9,400 per cubic millimeter, with 44% eosinophils, and the x-rays showed bilateral perihilar infiltrations.

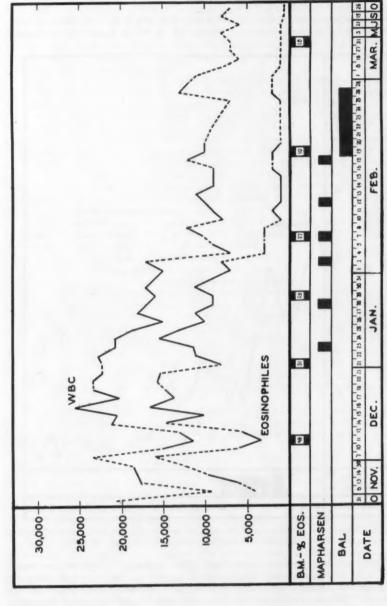


CHART 4. Depicting the changes in white cell and eosinophil counts with the intravenous administration of oxophenarsine (Mapharsen) and the failure of Dimercaprol (BAL in oil) to alter the eosinopenic effects of arsenic (case 5).

Although the patient was discharged asymptomatic on November 15, the symptoms reappeared three days later. She was re-admitted on December 9 in status asthmaticus, with progression of the perihilar infiltrations and eosinophilia. Treatment with bronchodilators led to clinical improvement, and she was discharged on December 22. She was re-admitted on January 17, 1952, at which time the red cell and hemoglobin determinations were within normal limits, and the white cell count ranged from 12,000 to 26,000 per cubic millimeter, with actual eosinophil counts of from 2,500 to 16,000 per cubic millimeter. The bone marrow was heavily infiltrated with eosinophilic elements (49%). Her stools were positive for ova of N. americanus, for which she received crystoids of hexylresorcinol (Caprokol). Following treatment, 14 consecutive stool examinations failed to show hookworm ova but were positive for T. trichiura, T. spiralis and S. mansoni skin tests were negative, and three rectal biopsies failed to show either viable or dead eggs of S. mansoni. The blood was negative for microfilariae or malarial parasites. The blood Kahn test was negative, and the heterophil antibodies and cold hemagglutinins were absent. The erythrocyte sedimentation rate was accelerated (up to 43 mm. in one hour), and the total serum proteins were 7.57 gm.%, of which 4.08 gm.% were globulins.

In view of the progressive deterioration, the patient was given 40 mg. of oxophenarsine (Mapharsen) intravenously every five days for six doses, starting on January 23. There was rapid general improvement, and she was asymptomatic by January 30. This was accompanied by a rapid and progressive diminution of circulating eosinophils (chart 4). The administration of BAL in oil (Dimercaprol) in divided intramuscular doses of 4 mg. per kilo of body weight every four hours for eight days failed to alter the rapid dissolution of the eosinophils.

The chest x-rays were normal by February 20, and normal eosinophil levels were attained by March 27, by which time she had had a 15 pound weight gain. The bone marrow, the serum proteins and the sedimentation rate had gradually reverted to normal, and during the last two years she has been totally asymptomatic.

COMMENTS

The data presented in this paper would indicate that infiltrative eosinophilia is not exclusively a tropical disorder, that it predominates in the white race, that it may occur at any age, and that it is not specifically related to work or other habits.

The onset may be either insidious or acute but, once established, the disease shows an invariable tendency to chronicity. The acute onset may be characterized by a violent attack of asthma with fever which may require heroic therapeutic measures. The insidious onset is characterized by lassitude, weakness, general malaise, weight loss, paroxysmal cough with scanty sputum, slight dyspnea, wheezing respiration and low grade fever. The physical examination may be completely normal, aside from moderate to severe pulmonary emphysema, malnutrition, and occasional wheezes, rhonchi and râles, especially when the patient is examined in the morning. The liver, spleen and lymph nodes may be enlarged.

Although the presenting symptoms are generally referred to the lungs and dominated by asthmatic manifestations of variable severity, it must be emphasized that we are dealing with a systemic rather than an exclusively pulmonary disorder. Thus, hospitalization may be prompted by symptomatology pointing to a pathologic process in the gastrointestinal tract, the lymphatics or the joints. In a few instances the condition may be discovered by the routine blood studies in cases suffering with other unassociated illnesses, but in most of these cases there is a history of asthma of variable severity and duration.

The course and duration of the illness are variable. In some instances with an acute onset the severe clinical manifestations may persist for no more than two weeks, with spontaneous recovery. In others, frequent exacerbations of the pulmonary symptoms may appear at variable intervals for as long as 20 years or more. In most instances the asthmatic symptoms are precipitated by upper respiratory infections; in others, there are no recognizable precipitating factors.

It has been shown that allergic rhinitis, spasmodic bronchial asthma and other forms of allergy may precede and accompany the infiltrative eosinophilia. However, the persistence of the asthmatic manifestations in spite of a normal hemogram and bone marrow following arsenical therapy would suggest that, in some instances, spasmodic bronchial asthma may be pathogenetically different from infiltrative eosinophilia. Postmortem observations in Loeffler's syndrome indicate that the bronchial walls are edematous and heavily infiltrated with eosinophils, and that there is marked exudation in their lumina. But it must be emphasized that in infiltrative eosinophilia the bronchial muscle elements do not undergo hypertrophy, as in spasmodic bronchial asthma.

The important rôle of the pulmonary eosinophilic infiltrations in perpetuating the asthmatic symptoms must be emphasized. Beneficial response to arsenical therapy, as shown by the disappearance of the asthmatic symptoms and the correction of the eosinophilia, should be expected in even the most advanced cases of the disease (20 years or more). However, it seems as though a complete clinical recovery should be expected only among those cases of infiltrative eosinophilia uncomplicated by spasmodic bronchial asthma.

The rôle of the extensive vascular lesions, indistinguishable from polyarteritis nodosa, and the "eosinophilic pneumonia," at times accompanied by fibroblastic proliferation ("unresolved eosinophilic pneumonia") in the production and the perpetuation of the pulmonary manifestations, remains unassessed. The favorable clinical response to arsenical therapy, including the disappearance of the pulmonary alterations, would indicate that the drug may radically alter the vascular lesions. There is evidence to suggest that the administration of arsenic leads to organization of the granulomatous lesions of the liver.⁴¹

That the disease may be experimentally produced in man has been demonstrated in case 2. It seems as though, in this instance, the condition was precipitated by a violent antigen-antibody reaction in a preëxisting allergic state. This disturbance can best be interpreted on the basis of a

diffuse vascular disorder which persisted for 19 months. It was evident that, while the acute infiltrative eosinophilia responded favorably to arsenic, the more chronic allergic state remained unchanged.

The clinical and pathologic similarities of polyarteritis nodosa with diffuse pulmonary eosinophilic infiltration and infiltrative eosinophilia would suggest a common pathogenesis. In addition to the pathologic evidence, 18, 42-45, 47 a common pathogenesis is further substantiated by the presence of renal disease and hypertension in some of our cases. These may indicate diffuse vascular damage in the kidney as well as the liver and lungs. Besides, the high incidence of fever, weakness, lassitude, weight loss, and gastrointestinal disturbances in the presence of allergy would militate in favor of involvement of multiple organs and systems. The splenomegaly, the generalized lymphadenopathy and the hyperglobulinemia, with predominance of the gamma globulins, would point to a violent hypersensitivity state produced in man by numerous and variable allergens. Thus it appears as though infiltrative eosinophilia represents a phase, modality, stage or gradient of the hypersensitivity state. The clinical manifestations may be either mild or severe, depending upon the degree of tissue reactivity, the intensity of the stimulus, and the organs affected.

The very limited and, at times, undiscernible eosinophilic dissolution following the parenteral administration of corticotropin (Thorn test) remains unexplained. It seems as though, in this condition, the response of the adrenal cortex is rather inefficient. Adrenal cortical depression from constant, unrelenting stress imposed by the continuous hypersensitivity state may be a contributory factor.

The prompt and extensive decreases in the circulating eosinophils following intravenous typhoid vaccine are worthy of comment. The maximal eosinopenic effects occurred within the first 30 minutes after the injection of the pyrogen and prior to marked increases in rectal temperature. The more delayed and less marked eosinopenic effects of intravenous corticotropin and hydrocortisone * would support another mechanism than the stimulation of the adrenal cortex as the most important factor in the dissolution of the eosinophils following the intravenous administration of typhoid vaccine. The results further suggest that the eosinopenic effects of parenteral corticotropin and cortisone are less effective than those of typhoid vaccine. Whether the sequestration of eosinophils in the lungs and other viscera is a contributory factor in the reduction of the circulating eosinophils that follows the injection of a pyrogen remains a moot question.

The eosinophilic hyperplasia of the bone marrow remained unaffected by the use of corticotropin and typhoid vaccine, but was radically depressed by arsenical preparations, suggesting different modes of action. While with prolonged corticotropin therapy there was rapid dissolution of circulating

^{*} Hydrocortone (brand of hydrocortisone) produced by Merck and Co., Inc., Rahway, New Jersey.

eosinophils with no bone marrow alterations, with arsenic the decrease in the peripheral eosinophilia was proportional to the bone marrow depression.⁴¹

The inability to demonstrate bacterial pathogens in cultures of sputum obtained through the bronchoscope would lend support to other than a bacterial etiology. This is further substantiated by the failure of antibiotics to alter the acute or chronic phases of the disease. The asthmatic manifestations and the eosinophilia responded favorably to arsenical therapy in spite of the persistence of sinusitis of bacterial origin. It must be emphasized that the eradication of a sinus infection may fail to correct the asthmatic manifestations or the eosinophilia.

It is evident that in this paper we are not dealing with the chronic infiltrative eosinophilia associated with parasitic infestations. Thus, it was shown that the complete eradication of the parasitic infestations failed to alter the course of the disease, whereas treatment with arsenic led to clinical recovery from the hypersensitivity state in spite of the constant parasitism. Our limited knowledge of the reaction of the host to parasitic infestations does not warrant definite conclusions as to their rôle in the production of infiltrative eosinophilia amenable to arsenic. However, we have shown that the hypereosinophilia of severe infestations with S. mansoni, A. lumbricoides and N. americanus is unaffected by arsenic therapy. 46 In studies on acute Manson's schistosomiasis in man, it has been demonstrated that both the hypereosinophilia and the clinical picture remain unaltered by specific therapy, rendering a violent hypersensitivity state with hypereosinophilia as the most probable underlying mechanism of the earliest symptoms. It seems reasonable to assume that the variant of infiltrative eosinophilia arising from parasitic infections differs from that under discussion. However, it must be emphasized that the eosinophilic response varies from person to person, and that the violence and severity of this response are not always dominated by the extent of the parasitic infection.

The rôle of syphilis as a causative factor lacks clinical support. However, a false-positive Wassermann reaction may be commonly observed. This can best be attributed to the altered serum globulins, representing an alteration which accompanies the hypersensitivity state. The reduction of the total serum proteins and the gamma globulin fraction following the administration of arsenic remains unexplained. The absent heterophil antibodies and cold hemagglutinins would tend to support other than a viral etiology. The negativity of other serologic tests minimizes the etiologic rôle of the common bacterial pathogens. It must be emphasized that the radiologic picture is at times so similar to miliary tuberculosis that every effort should be made to eliminate this possibility, and that, although it appears that *M. tuberculosis* is not etiologically related to infiltrative eosinophilia, pulmonary tuberculosis may accompany the disease.

The absence of eosinophils from the urinary sediment, spinal fluid or vaginal secretions, with a hyperabundance in the sputum, remains unex-

plained. There is enough pathologic evidence to prove that the inflammatory reaction accompanied by eosinophilic infiltration may occur in numerous organs besides the lungs and liver.^{18, 42-45, 47}

The demonstration of granulomatous lesions in the liver is a subject for speculation. In spite of the frequent hepatic enlargement in our series of cases, the liver function tests were generally within normal limits. Whether the hepatic pathologic alterations are due to a specific etiologic agent or represent a manifestation of generalized hypersensitivity (extravascular granulomatous lesions) remains unassessed. The lymph node biopsies showed diffuse hyperplasia with eosinophilic infiltration, suggesting an allergic response. The absence of vascular lesions in the appendix of one of our patients does not eliminate the possibility of vascular alterations elsewhere in the body.

SUMMARY AND CONCLUSIONS

An analysis of the data derived from the clinical study of 33 cases of infiltrative eosinophilia would indicate that we have dealt with a variant, gradient, stage or modality of the hypersensitivity state. The condition is in many respects indistinguishable from polyarteritis nodosa with diffuse pulmonary eosinophilic infiltrations. The severity of the clinical manifestations generally depends upon the extent of the field of sensitivity (organs or system affected) and the severity of the inflammatory reaction. Evidence is presented to demonstrate that the exact etiologic agent is elusive, and that the rôle of parasitic causation should be doubted in the arsenic-sensitive group.

It appears that the poor eosinopenic response to corticotropin in violent hypersensitivity states may best be explained on the basis of the adrenal cortical depression that accompanies the underlying, unrelenting stress. The eosinopenic responses to arsenic, typhoid vaccine and cortisone are governed by different mechanisms.

The radical and rapid eosinopenic response to intravenous typhoid vaccine is explained by other mechanisms than the stimulation of the already depressed adrenal cortex. The beneficial effects of arsenical therapy remain unexplained. Its eosinopenic effects do not appear to depend upon the paralysis of the SH groups. The administration of arsenicals leads to a depression of the production of eosinophils by the bone marrow. Parenteral typhoid vaccine, cortisone and corticotropin fail to alter the bone marrow picture.

Because of the failure to demonstrate the exact etiologic agents, and the elusiveness of the function of the eosinophil, infiltrative eosinophilia must remain in the allergic circle. A better understanding may perhaps be achieved by avoiding categorization, and by grouping all conditions characterized by diffuse vascular disease with profuse infiltration with eosinophils, and a circulating hypereosinophilia, under a common, descriptive term.

SUMMARIO IN INTERLINGUA

Es presentate un analyse del constatationes clinic e de studios laboratorial in 33 casos de eosinophilia infiltrative. Le series consisteva de casos in que responsas favorabile al tractamento con varie formas de arsenico habeva essite demonstrate. Variationes in le declaration del symptomas es describite. Le declaration es ramente de character acute con symptomas predominantemente respiratori. Illo es plus communmente gradual con malaise, anorexia, e leve molestias pulmonar. Il etiam ha casos que es asymptomatic. Le curso del morbo pote esser breve o extender se a transverso multe annos.

Eosinophilia infiltrative es un variante, un stadio o un modalitate del stato de hypersensibilitate e in multe respectos es indistinguibile de polyarteritis nodose con diffuse infiltrationes pulmonar. Le manifestationes clinic depende del organos afficite e del severitate e magnitude del reaction inflammatori. Un etiologia parasitic pare dubitose in le forma arsenico-sensibile.

Le responsas eosinopenic que es evocate per arsenico, vaccino typhoide, e cortisona es governate per differente mechanismos. On ha le impression que il occurre un depression adrenocortical accompaniante le subjacente perdurative stress del eosinophilia infiltrative.

Le effectos benefic del therapia a arsenico remane inexplicate. Su effectos eosinopenic non para depender del paralyse del gruppos SH. Durante que le arsenicales produce un depression del production de eosinophilos in le medulla ossee, parenteral vaccino typhoide, cortisona, e corticotropina non affice le evenimentos in le medulla ossee.

Proque il non es possibile demonstrar le exacte agentes etiologic de eosinophilia infiltrative e proque le function del eosinophilos remane elusive, iste morbe debe ancora esser considerate como pertinente al circulo del conditiones allergic. Un meliorate comprension de eosinophilia infiltrative pote esser obtenite si on evita su categorisation e si on gruppa omne conditiones con diffuse morbo vascular accompaniate per profuse infiltrationes eosinophilic e un eosinophilia del circulation sub un termino descriptive commun.

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THE DILEMMA OF THE NONTOXIC NODULAR GOITER*

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PURPOSE

The purpose of this paper is to summarize the experience of some of the major clinics in the United States relative to the frequency of carcinoma of the thyroid in association with nontoxic nodular goiter, and to present a series of cases from a large Army hospital. In addition, we shall attempt to point out the difficulty of interpreting the wealth of material now in print on the subject. The problem of whether the presence of symptoms would render the individual case more likely to have cancer, a facet which has received little attention in the literature, was carefully analyzed.

MATERIAL

The case records of all patients having the discharge diagnosis of non-toxic nodular goiter and carcinoma of the thyroid were reviewed for the five year period of 1950–1954, inclusive. All cases of carcinoma were found in association with nodular goiter, none in diffuse goiter. All cases must have had surgery to be included in the series, so that the exact pathologic diagnosis was known. The report of the Armed Forces Institute of Pathology was available in each case. It was realized at the onset that the series would be a selected group, because the records were those of in-patients who had been operated upon, and physician-screening had thereby occurred in the out-patient section, as well as on the in-patient service prior to referral to surgery.

The patients in the series were all active or retired military personnel and their dependents.

METHOD

Each record was carefully analyzed and the patient placed in one of five groups, as follows:

- 1. Benign goiter without symptoms: patient hospitalized for another complaint.
- 2. Benign goiter without symptoms: found on routine physical examination in the Outpatient Department.

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- 3. Benign goiter with symptoms.
- 4. Carcinoma with symptoms.
- 5. Carcinoma without symptoms: found on examination while patient was hospitalized for another complaint.

The age and sex of all patients, the type of operation performed and, finally, the accuracy of the physician in determining the number of nodules present in a given gland were noted.

RESULTS

The average age of the entire group was 39.2 years, the average age of the patient with benign lesions was 41.1 years, and the average age of the patient with carcinoma was 33.2 years.

Table 1 shows the number of patients in each of the aforementioned subgroups. There were 40 benign asymptomatic goiters, and four cases of

TABLE 1

	Classification of Patients		
	Destruction of the state of the		No. of Cases
1	Benign goiter without symptoms Patient hospitalized for other complaints		16
II	Benign goiter without symptoms Found on routine physical examination		24
III IV V	Benign goiter with symptoms Carcinoma with symptoms Carcinoma without symptoms		98 23 4
		Total	165

asymptomatic cancer. There were 98 cases of symptomatic benign goiter, and 23 cases of symptomatic cancer. It is noteworthy that the most prominent complaint in all symptomatic cases, benign or malignant, was merely the known presence of a painless lump in the neck. Pressure symptoms such as hoarseness, dysphagia and dyspnea were not important in differentiating cancer from benign lesions in this series. More patients with benign lesions had these complaints than did those with cancer.

Table 2 depicts the breakdown of cases by age and sex. It is noted there was a 4:1 female-to-male incidence of goiter in the entire series. There was a 3:1 female-to-male incidence in the group with carcinoma, showing that, though goiter is more common in the female, there is a slightly greater possibility that the goiter in the male is malignant.

Table 3 indicates that the frequency of carcinoma in the entire series was 16.4%. The frequency of carcinoma in patients with symptoms (painless mass in the neck) was 19.0%, and in those without was 9.1%. This observation was subjected to statistical analysis, and it was found by applying the standard t-test of statistical significance that there was a 6% level

TABLE 2
Age and Sex Distribution
Males, 37; Females, 128

	10-	-19	20	-29	30	-39	40	-49	50	-59	60	-69	70-	-79	Tota
	M	F	М	F	M	F	М	F	M	F	М	F	M	F	Total
Benign goiter without symptoms Benign goiter with symptoms Cancer with symptoms Cancer without symptoms	1	1 2 2	2 4 1 1	4 16 8	4 3 3 1	5 29 3 2	3 5	9 16 1	2 3 1	6 12 1	1 2	3 5 2		1	40 98 23 4
Age group totals	1	5	8	28	11	39	8	26	6	19	3	10		1	

of confidence. There are then six chances out of 100 that the results (difference in per cent between the symptomatic and asymptomatic groups) could have occurred in this series by chance alone.

In table 4 we have noted the physician's accuracy in detecting whether the gland contained solitary or multiple nodules compared with the finding of the pathologist. All nodules recorded were gross nodules when examined

TABLE 3
Carcinoma Frequencies

Entire group	16.4%
Asymptomatic group	9.1%
Symptomatic group	19.0%

by the pathologist. We note the clinician to be only 48% accurate in predicting the single nodule.

Table 5 denotes the variety of surgical procedures which were carried out on 158 cases of benign goiter. Twelve general types of operations were performed. This variety of operations indicates a lack of conviction on the part of the surgeon as to the surgical procedure of choice.

TABLE 4
Clinician's Accuracy of Examination

Cimioni Directi	ary or emention	
	No. of Cases	% Accuracy
Stated: single nodule Found: multiple	67	
Stated: diffuse goiter Found: multiple nodules	4	52
Stated: single nodule Found: single	50	40
Stated: multiple nodules Found: multiple	17	48
Total	138	100%

Total

TABLE 5

Types of Surgical Procedures in 138 Cases of Benign Node	ılar Goiter
Subtotal lobectomy	38
Complete subtotal	38
Lobectomy	23
Nodulectomy	22
Lobectomy and isthmectomy	5
Subtotal lobectomy and isthmectomy	1
Isthmectomy	3
One half both lobes	2
Nodulectomy and isthmectomy	2
Lobectomy and nodulectomy	2
Partial lobectomy, isthmectomy and nodulectomy	1
Complete thyroidectomy	1

DISCUSSION

In recent years the frequency of carcinoma in nodular goiters has been reported to be alarmingly high (table 6).1-18 Most authors agree that the manner of selection of cases by the physician, as well as self-selection by the patient, may be of some importance in the statistical results of their respective series. 1, 7, 14, 15 Sokol 18, 16 points out the hazards of interpreting the data now in print and, by creating a hypothetic population, has determined that the true incidence of cancer in nontoxic goiter should be only about 0.2%. Miller 17 found 3.7% unsuspected cancer in nodular goiter, and stated that estimates of 0.2 to 0.4% represent a more nearly true incidence. He further points out that the data obtained from pathologic and surgical material are not reliable in presenting the true statistical behavior of nodular goiter as a potentially precancerous lesion. Meissner and McManus 18 state that the great discrepancy between the incidence of papillary structure in benign and that in malignant states suggests that perhaps most papillary carcinomas are malignant from their inception and do not arise from a preëxisting benign phase.

Selection of patients by the physician is extremely important in shading the statistics in favor of nodular goiter's being precancerous. The patient

Table 6
Frequency of Carcinoma in Nontoxic Nodular Goiter in Several Large Series

	Cases of Nontoxic Nodular Goiter	Cancer	Solitary Nodule % Cancer
Cattell and Colcock, Boston®	748	10.20	33,30
Majarakis, Slaughter and Cole, Chicago ¹⁸	448	15.60	20.90
Crile and Dempsey, Cleveland ¹	247	10.90	24.50
Ward, San Francisco ¹⁰	3,539	4.80	15.60
Beahrs, Rochester ⁴	3,121	3.80	
Cerise et al., New Orleans	210	17.30	19.80
Beal, Los Angeles®	133	3.75	5.00
Miller, Detroit ¹⁷	435	3.70	4.00

is guilty, too, since he often does not appear at the doctor's office unless the gland is growing or there is some functional activity of the gland.¹ Most patients are first seen by the general practitioner or the internist, and here the first element of selection occurs, since those glands that are questionable and those readily identifiable as cancer are quickly referred to the surgeon. Small nodules are often passed by for routine follow-up or to be forgotten. The higher the referred practice of an individual reporting statistics, the less likely those statistics are to represent what the average practitioner sees.¹¹ Crile and Dempsey¹ state that the general physician feeling the nodule notes it to be soft and multinodular and hence discourages operation. Once the patient is seen by the surgeon, further selection often occurs, depending upon that surgeon's opinions and criteria.

It is noted that the frequency of carcinoma in the series reported here is 16.4%. We should like to point out, however, that Letterman Army Hospital is an evacuation center for a large Army geographic area and thus receives complicated cases. Those glands that are operated upon elsewhere and found to be benign are not transferred to this hospital, whereas those found to be malignant are. Eight cases of carcinoma in the series were referred with that diagnosis. The same problem exists for other large

hospitals and clinics, civilian or military.

We feel it to be important, in shading the statistics in favor of nodular goiter's being a precancerous lesion, that those patients with symptoms are more likely to appear in the physician's office, and that these are the patients most likely to have cancer. The great majority of nodular goiters are the asymptomatic ones that are never seen by a physician. The latter goiters. too, are less likely to be carcinoma. In the series reported here the frequency of cancer in patients with symptoms relative to the neck who had nodular goiter was 19.0%, whereas the frequency of cancer in asymptomatic goiters was 9.1%. Twenty-four cases were operated upon who were found to have goiter at the time of a routine physical examination when the patient was completely asymptomatic. Not one had cancer. The four cases of cancer in patients without symptoms referable to the neck were found when the patients were hospitalized for other problems (one duodenal ulcer, one pneumonia, one hepatitis, and one possible intervertebral disc) and found to have a goiter and subjected to thyroid surgery. From the trend in this small series it seems possible that the frequency of carcinoma in nontoxic nodular goiter may be as high as has been reported in many series in those patients with symptoms relative to the thyroid, but is low in those patients without symptoms. Hence, the over-all frequency of cancer in nodular goiter may be far lower than 15 to 16%, and may approach Sokol's estimate of 0.2%.

The frequency of nodular goiter at autopsy has been reported to be from 4.5 to 88%, 19-28 depending upon where, geographically, the series was accumulated. Wegelin, 24 reporting on a clinical survey in Switzerland, states

that one-half of the persons over 20 in Berne have nodular goiters, and that it is uncommon not to find nodules in the glands of persons over 60. Vander et al.²⁵ in a very important study, examined 5,234 unselected patients in a nongoitrogenous region and found that 3.0% (159) had isolated nontoxic thyroid nodules. Twenty-eight cases were operated upon and no carcinomas found. The entire group will be followed for future developments as to cancer, new nodules, etc. Fifty-nine cases (1.1%) of multiple nontoxic nodules were found. Four were operated upon and were found not to have cancer.

The frequency of carcinoma of the thyroid as found at autopsy has been reported to be about 0.1% of all autopsied cases and about 0.56% of all autopsied cancer cases. Vanderlaan found five cases of carcinoma of the thyroid in 18,668 autopsies. Cole states that the reason for such a low incidence of carcinoma of the thyroid at autopsy is that patients with carcinoma of the thyroid so often die at home and autopsy is not performed. Sokol states that he feels this is not true, and that patients with those diseases in which there is considerable interest and active investigation are more apt to be hospitalized and autopsy is more apt to be performed, in contrast to the more common conditions, such as cerebrovascular accident.

From the apparent discrepancy between the frequency of nodular goiter found at autopsy and that in clinical studies, it seems difficult to accept the

present concept that 10 to 15% of nodular goiters are carcinoma.

Though it is widely accepted that the presence of a solitary nodule in the thyroid is of considerable importance as a potentially precancerous lesion, ^{3, 5-7, 9, 11, 18, 14, 27-29} it is noteworthy that the series reported here, as well as other reported series, ^{2, 4, 30} points out the unreliability of the physician in the detection of the exact degree of nodularity of a given gland. Therefore, this clinical criterion for potential malignancy cannot be applied with any degree of reliability.

Ravdin ⁸¹ states that carcinoma of the thyroid cannot be expected to present fixation or unusual firmness with any regularity. Ward ⁶ states that there are no pathognomonic signs of early cancer of the thyroid. Cattell and Colcock ⁹ found that the preoperative diagnosis of cancer of the thyroid was less than 50% accurate. Crile,²⁷ on the other hand, states that if a high index of suspicion is maintained, the diagnosis of carcinoma should be accurately made preoperatively in 90% of cases. The important criteria for diagnosis, in his opinion, are the consistency of the nodule, which is usually hard in carcinoma, the age of the patient, which is usually young, and the solitary nature of the nodule.

The surgeon attacking the problem of nodular goiter should have some convictions as to the nature of the lesion he is treating. Crile and Dempsey ¹ state that surgeons should accustom themselves to thinking of thyroid tumors at the time of operation not as adenomas that may become malignant, but as possible cancer, and that extirpation should be complete. Crile fur-

ther states 27 that an adenoma worth removing at all should be treated by lobectomy. He adds that partial lobectomy is apt to result in incomplete removal of the tumor, and that there may be recurrences. Rogers 29 points out that lesions may develop in glands already treated surgically, and that recurrences are not uncommon. He does not recommend prophylactic removal of all nodules, but states that solitary nodules in young people should be removed. Opinion is almost unanimous on this point. Cope recommends total thyroidectomy for multinodular glands. Schlesinger et al.21 recommend that all nodules be removed in patients under 50 years of age, realizing that in the age group of 30 to 50 years more are apt to be benign than in the group under 30 years. Nodules in the thyroids of patients over 50 are likely to be benign, since these nodules are usually on a physiologic basis. However, Beahrs 28 states that 35% of patients with papillary adenocarcinoma are 50 years of age or over. Beal 30 states that operation should be advocated in cases of nontoxic multinodular goiter, and urged in cases of solitary nodular goiter. Lahey and Hare 11 propose that prophylactic removal of all discrete adenomas would do much to lower, if not to abolish, the occurrence of cancer of the thyroid.

The present trend in the classification of thyroid carcinomas based on microscopic appearance or on their biologic behavior classifies them as either highly malignant, early metastasizing types, usually incurable by the time they are discovered, or the much less malignant type, which is slow to grow and late to metastasize. Microscopically, these tumors have been described as nonpapillary and papillary carcinoma, respectively. Perhaps, then, a period of observation, to ascertain any change in size or consistency in the nodular goiter, would not be detrimental to the patient.

Radioactive iodine, in addition to being a valuable tool in the diagnosis of hyperthyroidism and hypothyroidism, and in the treatment of certain cases, may be of assistance in the differentiation of carcinoma from benign nodular goiter. Perlmutter and Slater ³² recently reported a series of cases of nodular goiter in which nodules were classified as "hot" or "cold," depending upon whether their uptakes of I¹³¹ were more than that of a non-nodular area of thyroid tissue of the same patient. Of 87 "cold" nodules, 22 were malignant. With thyroid therapy, some of the "hot" nodules diminished in size.

Multinodular goiter in older individuals (40 plus) would seem to pose a somewhat different problem from that in younger persons because of the physiologic changes (especially in the female) which produce goiters in this age group.

It is evident that the problem of therapy of nodular goiter is a complex one, about which hard-and-fast rules cannot be laid down. Certainly any nodule that appears "suspicious" (presenting recent growth, symptoms of unusual hardness, or appreciable difference in consistency from the rest of the gland) should be surgically removed. The isolated nodule found on

clinical examination should be viewed with more suspicion than multinodular glands, because of the higher incidence of carcinoma. This fact, however, loses some weight because glands thought to contain a solitary nodule on clinical examination frequently are found to be multinodular when removed. Further study in large series of cases is warranted. Random sampling of the general population for nodular goiter in various age groups, with notation of sex, geographic location and signs or symptoms, requires careful evaluation. Long-term follow-up is necessary.

Conclusions

A series of 165 cases of nontoxic nodular goiter and carcinoma of the thyroid has been presented and inferences have been drawn from the group. Some of the conflicts in the literature relative to the frequency of carcinoma of the thyroid in nontoxic nodular goiter have been reviewed in order that the full magnitude of the problem could be realized.

From this study, it would seem that the following points can be made:

1. The frequency of carcinoma in nodular goiter is probably far lower than has been reported in most series or in this series, for the reasons stated.

2. The manner of selection of cases is largely responsible for the false picture currently depicting the frequency of carcinoma of the thyroid in non-toxic nodular goiter.

3. If the patient has symptoms he is more likely to have cancer when he is first seen.

4. Though it seems likely that carcinoma is more prevalent in those glands containing a solitary nodule (from surgical material), the physician's inaccuracy in detecting the number of nodules present in a given gland makes sole dependency upon such an observation unreliable.

5. Perhaps the use of I131 will be of assistance in the differentiation of

carcinomatous and benign nodules of the thyroid.

6. Until further long-term study clarifies this problem it would seem appropriate to recommend operation for most cases of nontoxic nodular goiter.

SUMMARIO IN INTERLINGUA

Esseva examinate le protocollos de 165 patientes con nontoxic struma nodular e carcinoma del glandula thyroide, originalmente vidite durante le periodo ab 1950 a 1954. Omne le carcinomas trovate esseva associate con struma nodular. Le frequentia de carcinoma in le serie esseva 16,4%. Iste valor esseva comparate (in Tabula 6) con le resultatos obtenite in altere clinicas. Tabula 3 indica que le frequentia de carcinoma in patientes con symptomas esseva 19% e in patientes sin symptomas 9,1%. Tabula 4 monstra que le clinico produceva in solmente 48% del casos un accurate evalutation preoperatori del ver grado de nodularitate (simple o multiple). Le varietate del operationes interprendite (Tabula 5) pare indicar un manco de conviction del parte del chirurgo in re le tractamento de election.

Nos ha tentate signalar le difficultate de interpretar le litteratura de iste thema. Le majoritate del autores opina que le maniera de selection del casos per le medico o le chirurgo (e erronee reportos per le patientes mesme) effectua un significative distorsion del resultatos statistic. Sokol insiste que le ver incidentia de carcinoma in struma nontoxic non deberea exceder 0,2%. In varie localitates le frequentia de struma nodular al autopsia ha essite reportate como amontante a diverse nivellos inter le extremos de 4,5 e 88%. In un studio importante, Vander et al. examinava 5.234 non-seligite patientes in un region non-strumigenic e trovava 3% con nontoxic nodulos thyroide. Iste gruppo va esser observate in su disveloppamento futur.

Le frequentia de carcinoma thyroide constatate al autopsia ha essite reportate como amontante a circa 0,1% de omne casos e a circa 0,56% de omne casos de cancere. Quando on considera iste valores e le datos relative al frequentia de struma nodular trovate al autopsia in studios clinic, il deveni difficile acceptar le conception currente que 10 a 15% de strumas nodular es cancerose.

Le tendentias presente pare favorir plus extense ablationes de histos thyroide que contine nodulos (o al minus lobectomia). Omne autores es de accordo que le nodulo solitari es plus periculose que nodulos multiple. On debe rememorar se que lesiones pote disveloppar se o pote recurrer in glandulas que ha jam essite tractate chirurgicamente.

Le currente modo de classification de carcinomas thyroide—multo maligne, precoce typo metastasante (usualmente incurabile al tempore de su discoperta), e un typo que es multo minus maligne e que cresce lentemente e comencia metastasar se tardivemente (usualmente papillari)—deberea requirer un periodo de observation clinic. Es discutite le question del etate del patientes, le desiderato de studios additional de longe duration in evalutar series seligite al hasardo in omne partes del population, e le uso de I¹⁸¹ in le determination de nodulos "calide" e "frigide."

Ben que le factores hic discutite pare indicar un multo minus alte incidentia de carcinoma in nodular glandulas thyroide, usque studios additional a longe duration pote clarificar le problema, il pare melio recommendar interventiones chirurgic in le majoritate del casos de nontoxic struma nodular.

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ACUTE BENIGN NONSPECIFIC PERICARDITIS WITHOUT A PERICARDIAL FRICTION RUB*

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Although acute benign pericarditis has long been known to the medical profession under many different designations, it was not until 1942, when Barnes and Burchell described their 14 cases of acute pericarditis of the nonsuppurative type, that interest in this disease was stimulated.¹ Recent years have witnessed an increased number of reports concerning the condition, and most observers have stressed its close resemblance to acute coronary occlusion with myocardial infarction.

It is extremely important to differentiate between acute benign pericarditis and myocardial infarction, because the prognosis and treatment of these two conditions are diametrically opposite. The former offers a good prognosis with complete recovery and no sequelae, whereas the latter carries with it a potential threat of limited activity or even early death.² Anticoagulant therapy, frequently resorted to in acute coronary occlusion, may prove fatal in acute pericarditis.

Clinically, the triad of symptoms, consisting of (1) precordial pain aggravated by coughing, breathing and bodily movement, (2) signs of infection, and (3) a pericardial friction rub, suggest the diagnosis of acute non-specific pericarditis. Definite extensive serial electrocardiographic changes out of proportion to the benign appearance of the patient confirm the suspicion.

The presence of a pericardial friction rub appearing early in the disease and lasting for several days is stressed by many authors as an important aid in the recognition of this syndrome. There are times, however, when this sign is not picked up. We have recently encountered five patients who presented the classic clinical picture, with serial electrocardiographic changes of acute nonspecific pericarditis, but in four of these a distinct pericardial friction rub could not be heard at any stage of the disorder. The purpose of this report is to present these cases.

CASE REPORTS

Case 1. A 24 year old white dental student was admitted to the University Hospital on January 29, 1954, complaining of pain in the chest aggravated by coughing and respiration, and of fever, lassitude, arthralgia and headaches of about three

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weeks' duration. There was no history of rheumatic fever, polyarthritis, chorea or a recent respiratory infection. The patient stated that he had been under a severe emotional strain at school for several months.

When first seen by his personal physician, on January 8, 1954, he complained of fever, sweating, pain in the chest and arthralgia, but no abnormal physical findings were apparent. However, the laboratory data revealed a polymorphonuclear leuko-

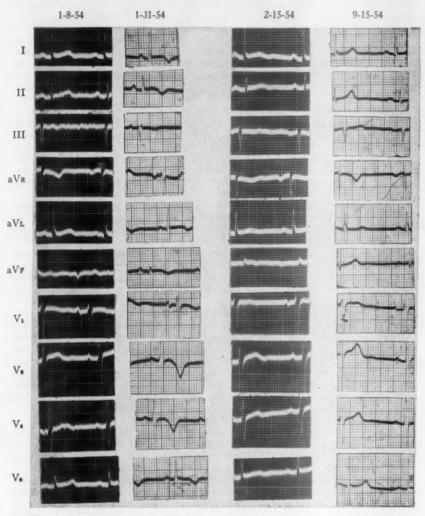


Fig. 1. Case 1. The tracing of 1/8/54 shows elevation of the ST segment in Leads 1, 2, V_s, V₄ and V₆. On 1/31/54 the ST segment is iso-electric, and there is marked inversion of the T wave in all the limb and precordial leads. On 2/15/54 the T waves have reverted to the upright position and the final tracing is completely normal.

cytosis and a sedimentation rate of 48 mm. per hour. An x-ray of the chest demonstrated slight enlargement of the heart in the transverse diameter and patches of increased density in the bases of both lung fields. The electrocardiogram showed elevated ST segments in Leads 1, 2 and V₂, with normal upright T waves in all leads (figure 1). The patient was given penicillin and Terramycin for several days without benefit, and a tentative diagnosis of acute rheumatic fever was made. Cortisone was therefore administered for one week, and within 36 hours an immediate clinical response was noted. Three days after cessation of steroid therapy, however, symptoms again developed, requiring his admission to hospital.

On admission the patient appeared quite comfortable, despite a temperature of 103.8° F. The heart rate was slow and the rhythm normal. There was a soft systolic murmur in the pulmonic area, but this disappeared in a few days. There was no pericardial friction rub, either at this time or throughout the entire course of his hospital stay. The lungs were clear on physical examination and the rest of the

findings normal.

Laboratory data disclosed a leukocytosis of the polymorphonuclear variety, a sedimentation rate of 73 mm. per hour, an elevated antistreptolysin titer, a negative tuberculin test, and a negative smear for L.E. cells. An electrocardiogram taken on January 31, 1954, revealed inverted T waves in all limb and unipolar leads except aV_R. An x-ray of the chest demonstrated a straightening of the left border of the heart, with a spherical cardiovascular silhouette and a small pleural adhesion at the right base. Two weeks later another x-ray showed a marked decrease in the cardiac size and a clearing of the pleural adhesion.

With symptomatic treatment and bed-rest there was gradual improvement, and on February 15, 1954, the patient was discharged in good health. An electrocardiogram taken at the time revealed a return of the ST segments to normal levels and upright T waves (figure 1). There had been no recurrence up to September 15, 1954, when he was last seen, and the electrocardiogram of that date was completely

normal (figure 1).

Case 2. A 52 year old male was admitted to the hospital on February 26, 1954, complaining of severe pain in the chest radiating to the left arm and aggravated by

respiration.

On physical examination the patient appeared acutely ill and slightly cyanotic, with some dyspnea and considerable diaphoresis. The temperature was 99° F.; pulse, 70; respiration, 20. The heart was not enlarged to percussion, the rhythm was regular, and no murmur or pericardial friction rub could be detected. A_2 was equal to P_2 , and the blood pressure was 150/90 mm. of Hg. The lungs were clear. The spleen and liver were not palpable, and there was no peripheral edema. The blood count was normal except for a slight leukocytosis, and the sedimentation rate was 19 mm. per hour. The electrocardiogram revealed a flattening of the T wave in Lead 1, slight elevation of the ST segment in V_1 , V_2 , a QS complex in V_1 and V_2 , and an inverted T wave in aV_L , V_2 and aV_4 (figure 2).

In view of the age, the pain in the chest and the early T-wave changes in several leads of the electrocardiogram, an initial diagnosis of acute coronary occlusion was entertained. The patient was therefore treated with Demerol, oxygen and Dicumarol. The following day his temperature rose to 101° F., but he appeared well and complained of being confined to bed against his will. The pain in the chest had disappeared, and 24 hours later the temperature returned to normal. The sedimentation rate had risen to 60 mm. per hour, and an electrocardiogram repeated on March 5, 1954, revealed inverted T waves in all leads except $aV_{\rm R}$ and $aV_{\rm L}$, a QS in $V_{\rm I}$ and an

increased r wave in V2 (figure 2).

The disparity between the widespread T-wave changes and the extreme well being of the patient, notwithstanding the elevated sedimentation rate, required a change in diagnosis to acute nonspecific pericarditis. As a result, anticoagulant

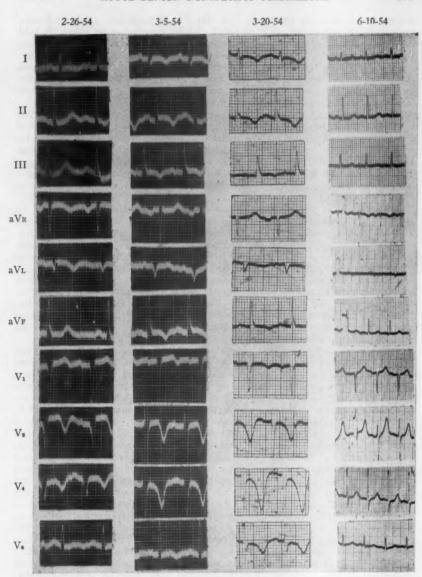


Fig. 2. Case 2. The tracing of 2/26/54 shows flattening of the T wave in Lead 1, slight elevation of the ST segment in V_1 and V_2 , a QS in V_1 and V_3 , and an inverted T wave in AVL, V_2 and V_4 . The tracing of 3/5/54 shows inverted T waves in all leads except aVR and AVL, a small r in V_1 and a taller r in V_2 . On 3/20/54 the T waves are more deeply inverted and the R wave in V_1 and V_2 is still small. The tracing of 6/10/54 has completely reverted to normal. Although the changes closely resemble those characteristic of a myocardial infarction, the clinical picture, physical findings and these progressive changes with reversion to status quo ante are consistent with pericarditis.

therapy was immediately withdrawn. On March 9, 1954, the patient left the hospital against advice. He visited one of us (M. L. G.) for examination on March 20, 1954, and stated that he had been up and about since his discharge and felt very well. An electrocardiogram showed inverted T waves in all leads except aV_R , similar to those observed previously (figure 2). The temperature and blood count were normal, but the sedimentation rate was 100 mm. per hour. Ten weeks later the electrocardiogram was completely normal (figure 2), and the patient was in good health, without having experienced any recurrence of symptoms or decrease in cardiac reserve.

Although the earlier electrocardiographic tracings resembled those of myocardial infarction, particularly the small r wave in the precordial leads, the reappearance of normal R waves in V_2 and V_4 and the clinical behavior of the patient favored the conclusion that pericarditis, with its underlying myocarditis, rather than both an anterior and posterior lateral wall infarction, was responsible for these changes. Patients with such extensive coronary artery involvement rarely present such a benign clinical appearance, nor do their electrocardiograms revert to their previous status in so short a time, if ever. 21

Case 3. A 44 year old dentist was admitted to the University Hospital on December 1, 1953, complaining of pain in the precordium radiating to the right arm and jaw, aggravated by respiration and changes in position. A history disclosed that 10 days prior to his present illness he had had an episode of fever, weakness and fatigue for which he received antibiotics. In three days he had recovered sufficiently to be able to return to his office.

Physical examination disclosed marked apprehension and diaphoresis. There was no dyspnea, orthopnea, cyanosis or peripheral collapse. The temperature was 100.2° F.; pulse, 100; respiration, 16. The heart was not enlarged to percussion. There were no audible murmurs or pericardial friction rub. The rhythm was regular and the blood pressure 120/80 mm. of Hg. The lungs were clear and the abdomen

was completely normal. Peripheral edema was absent.

The blood count was normal except for a polymorphonuclear leukocytosis, and the sedimentation rate was 84 mm. per hour. An electrocardiogram showed elevated ST segments in Leads 1, 2, aVL, V4 and V6. In addition, there was an R' and widened QRS complex to 0.10 second in V1, indicative of incomplete right bundle branch block (figure 3). A diagnosis of coronary occlusion was made, and the patient was treated with Demerol and Dicumarol. His temperature rose to 101.6° F. on December 3, 1953, and remained slightly elevated for two days. At the peak of the febrile state and thereafter the patient felt extremely well. Another electrocardiogram on December 12, 1953, revealed inverted T waves in Leads 1, 2, 3, aVL, aVF, V4 and V6 (figure 3). As it had now become evident that we were dealing with acute nonspecific pericarditis rather than a coronary occlusion, anticoagulant therapy was discontinued. The blood count was normal, but the sedimentation rate was still 54 mm. per hour. Frequent auscultation in the cardiac area failed to reveal any abnormal heart sounds or pericardial friction rub. The patient was discharged on December 25, 1953, and in a week returned to his dental practice. He was given check-ups for several months at weekly intervals and remained in good health. The electrocardiographic findings remained stationary until April 30, 1954, at which time they returned to normal, with persistence of incomplete right bundle branch block.

Case 4. A 51 year old white male was admitted to the University Hospital on November 10, 1953, complaining of severe chest pain radiating to both shoulders and aggravated by motion and respiration, as well as of chills and fever of two days' duration. The past history disclosed diabetes of 12 years' duration, adequately controlled by diet and daily administration of 35 units of PZI, peripheral arteriosclerosis, and a right bundle branch block, recently discovered electrocardiographically. The

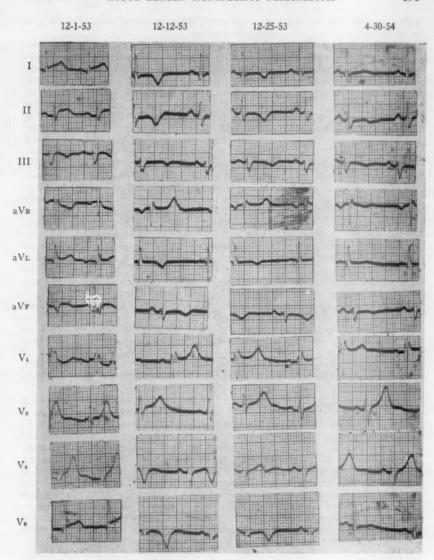


Fig. 3. Case 3. The tracing of 12/1/53 shows an elevated ST segment in Leads 1, 2, aVL, V_4 and V_6 . There is an R' and a widened QRS complex to 0.10 second in V_1 indicative of incomplete right bundle branch block. The tracing of 12/12/53 shows the ST segment back to the iso-electric level, inverted T waves in Leads 1, 2, 3, aVL, aVF, V_4 and V_6 , and no Q wave present. The tracing of 4/30/54 has returned to normal, with persistence of the incomplete right bundle branch block.

patient reported that he had been under considerable emotional strain for the past six months in an attempt to liquidate his business.

Physical examination revealed a temperature of 103° F.; respiration, 16; pulse, 78. There was a profuse diaphoresis, but no cyanosis, dyspnea or orthopnea. There was restriction of motion of the left chest. Cardiac dullness was enlarged to the left. The heart sounds were distant and the rhythm was regular. There were no audible murmurs or pericardial friction rub. The blood pressure was 140/80 mm. of Hg, and A_2 was greater than P_2 . There was definite dullness to percussion in the left lower chest posteriorly. The breath sounds were somewhat diminished in this area, and a few subcrepitant râles were heard. The liver was enlarged three finger-breadths below the costal margin, and the spleen was not palpable. The lower extremities felt cold to the touch, and the peripheral pulses were not detectable. There was no peripheral edema. The knee and ankle jerks were absent bilaterally, and vibratory sensation was markedly diminished. The sclerae appeared jaundiced.

Urinalysis disclosed a faint trace of albumin, 2.85% sugar and a slight trace of acetone, and on microscopic examination a few hyaline casts with several white cells and an occasional red cell were seen. The blood count was normal. The blood chemistry revealed 2 mg.% bilirubin, 18.5 mg.% urea nitrogen, 200 mg.% sugar, 150 mg.% cholesterol, 80 mg.% cholesterol esters, and 10.3 units alkaline phosphatase.

The blood culture, heterophil antibody and febrile agglutinin tests were all negative. The sedimentation rate was 101 mm. per hour. An x-ray of the chest disclosed enlargement of the heart in the transverse diameter but no abnormalities in the lung fields. The electrocardiogram demonstrated a right bundle branch block, with some elevation of the ST segment in several leads (figure 4).

Diagnosis at this time was difficult, but the differential diagnosis rested between lobar pneumonia with hepatitis and a pulmonary infarct. Neither of these conditions adequately explained the elevated alkaline phosphatase. Hence the possibility of a common duct stone with acute cholecystitis was entertained, but for a short time only.

The patient was placed on tetracycline therapy and given a proper diabetic diet, with an adequate amount of insulin. In three days the temperature gradually returned to normal and the patient felt markedly improved.

On November 18, 1953, however, he was again seized with severe, oppressing pain in the lower chest, aggravated by breathing and bodily movements, with a severe chill, marked sweating and peripheral collapse. There were marked cyanosis, dyspnea and an irregular, rapid heart rate which, on electrocardiographic examination, proved to be auricular fibrillation. The blood pressure was unobtainable. Oxygen, Demerol and Levophed were given at once, and within a short time the blood pressure rose to a normal level. Intravenous Digoxin was administered, and in about 30 minutes the ventricular rate became normal. The following day an electrocardiogram showed, in addition to the known right bundle branch block, an elevation of the ST segments in several leads. The pain in the chest continued for two days, and throughout this period frequent examinations failed to reveal any pericardial friction rub. The temperature returned to normal within 48 hours, and the patient once again felt well.

At this time the blood count indicated a slight leukocytosis, and the sedimentation rate was 101 mm. per hour. The liver function tests were normal. An x-ray of the chest on November 23 disclosed enlargement of the heart in the transverse diameter, and an area of density in the left base suggesting the presence of fluid. The electrocardiogram showed a broad Q wave in aV_L, with persistent elevation of the ST segment in V_4 and V_5 , and a flat T wave in Lead 2 (figure 4).

Twelve days later the patient again developed severe, oppressive pain in the chest aggravated by breathing and motion, chills and a temperature of 102° F., but there was no collapse or disturbance in the cardiac rhythm. The heart sounds were

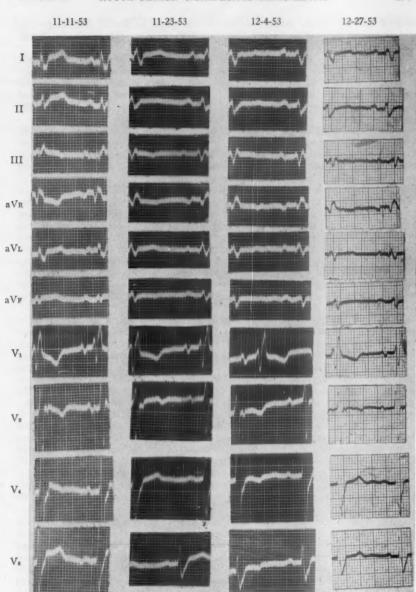


Fig. 4. Case 4. In addition to the right bundle branch block, the tracing of 11/11/53 shows elevation of the ST segment in Leads 1, 2, V_4 and V_5 . On 11/23/53 a broad Q wave appears in aVL, with persistent elevation of the ST segment in V_4 and V_5 , and a flat T in Lead 2. On 12/4/53 the T waves become inverted in the precordial leads. On 12/7/53 the T waves return to the upright position but the right bundle branch block persists.

of good quality, and no pericardial friction rub could be heard. The lungs still revealed slight dullness at the left base, but there were no changes in the breath sounds, nor were any râles audible.

The pain in the chest and fever subsided in about 48 hours, and the patient appeared exceptionally well. An electrocardiogram on December 4, 1953, disclosed inverted T waves in all the precordial leads and a return of the ST segment to the iso-electric line, consistent with pericarditis (figure 4). A chest x-ray demonstrated a decrease in the transverse diameter of the heart and clearing of the density of the left lung.

On December 12 the patient was discharged completely improved. Two weeks later he was reëxamined, and the electrocardiogram showed a return of the T waves to the upright position, as well as the old bundle branch block. Continued observation disclosed no further recurrence of acute pericarditis, and the patient returned to his usual work without any diminution in cardiac reserve.

Case 5. A 30 year old white male was admitted to the University Hospital on March 29, 1955, because of severe precordial pain and collapse. The previous day he had awakened with a sharp pain in the substernal region radiating to the abdomen and aggravated by motion and coughing. He noted considerable sweating and chills throughout the day, and a temperature of 102° F. The next morning he visited his physician and while there suddenly collapsed. He was given Demerol and oxygen and sent to the hospital with a diagnosis of acute myocardial infarction. The history revealed that several months before he had injured his left chest, fracturing the seventh rib, which had healed well, and that two weeks previously he had been confined to bed with a mild upper respiratory infection. He denied rheumatic fever or contact with tuberculosis.

On physical examination at the time of admission the patient appeared to be in mild distress and somewhat apprehensive but not in shock. No cyanosis or dyspnea was apparent. His temperature was 99.4° F.; pulse, 80; respiration, 14 per minute. The cardiac dullness was not enlarged to percussion. The rhythm was regular, and no murmur or pericardial friction rub could be heard. The blood pressure was 110/70 mm. of Hg. The liver and spleen were not palpable, and there was no evidence of peripheral edema. Several hours later a definite systolic and diastolic pericardial friction rub was audible at the fourth interspace to the left of the sternum. An electrocardiogram disclosed marked elevation of the ST segments in Leads 1, 2, 3, aV_L, aV_F and V₂ through V₆, with depression of the ST segment in aV_R. The following day an x-ray of the chest showed enlargement of the heart in the transverse diameter and widening of the superior mediastinum on the right side. The blood count was normal except for a polymorphonuclear leukocytosis.

On March 30 the temperature rose to 101° F., remained elevated for two weeks, and then returned to normal. The sedimentation rate on that day was 55 mm. per hour. It rose to 105 mm. on April 21 and dropped to 28 mm. at the time of his discharge from the hospital.

On April 5 the patient developed pain in the left chest extending into the axillary region, a cough and marked dyspnea, with slight cyanosis. At this time percussion revealed an increase in the cardiac dullness at the base, more pronounced on lying down, and dullness in the left lung field posteriorly, with flatness and diminished breathing in that area. The liver was palpable two fingerbreadths below the costal margin and was extremely tender. Another chest film showed marked increase in the cardiovascular shadow, with pleuropericardial adhesions at the left base. The transverse diameter of the heart was 19 cm., as compared with 16.5 cm. observed in the previous x-ray.

The liver function tests disclosed a normal cephalin flocculation; thymol tur-

bidity, 0.5 unit; total proteins, 6.4 mg.%, with albumin, 4.1 mg.% and globulin, 2.3 mg.%.

The heterophil antibody, C-reactive protein and cold agglutinin determinations were normal, but the antistreptolysin titer was elevated. A number of blood cultures were negative, and skin tests with several dilutions of old tuberculin failed to elicit a positive response.

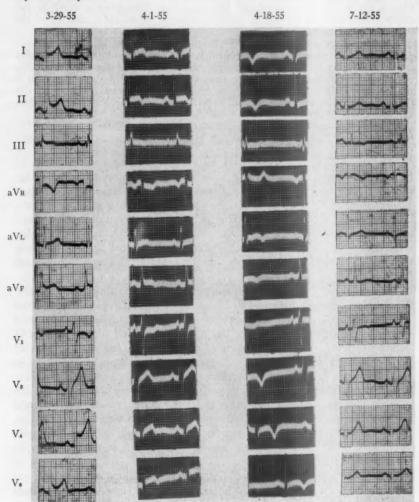


Fig. 5. Case 5. The tracing of 3/29/55 shows marked elevation of the ST segment in Leads 1, 2, aVF, Va, aV V4, and V4. On 4/1/55 there is slight inversion of the T waves in several leads, and a return of the ST segment to the iso-electric line. On 4/18/55 the T waves are deeply inverted. There are no Q waves. The final tracing of 7/12/55 is completely normal.

Serial electrocardiograms disclosed the typical progressive changes compatible with acute pericarditis, i.e., a return of the ST segment to the iso-electric level and inversion of the T waves in Leads 1, 2, aV_L , aV_F , V_4 and V_6 , but no Q waves (figure 5).

Throughout the first two weeks of the patient's hospital stay he was treated with aspirin, and during the third week he was given 600,000 units of penicillin, without any unusual dramatic effect. An x-ray of the chest taken on April 21 disclosed a diminution of the cardiac shadow to normal limits and a clearing of the left pulmonary density.

The patient improved considerably after the third week of his illness and was discharged on the twenty-seventh hospital day. He was seen subsequently at weekly intervals and gave no history of recurrence of the pain in the chest or fever. Repeated electrocardiograms continued to resemble the one taken on discharge, and it was not until July 18, 1955, that the findings reverted to normal. During all this time the patient was well and continued to perform the same arduous labor as before his illness.

COMMENT AND DISCUSSION

The cases described above were all males whose ages varied from 24 to 52. Two gave a history of previous respiratory infection, and two appeared to have undergone some emotional strain. Three presented a benign aspect throughout. One patient (case 4), during a recurrent acute episode, demonstrated a shocklike picture from which he recovered dramatically and appeared not too seriously ill. Another patient (case 5), in whom the disorder was ushered in by peripheral collapse which lasted but a short time, complained very little afterwards, despite considerable cardiopulmonary involvement.

The duration of the disease varied from two weeks to almost two months. The clinical features common to all consisted of: (1) pain in the chest aggravated by breathing and motion; (2) chills and fever; (3) mild leukocytosis at the outset, lasting for a variable period of time; and (4) persistent elevation of the sedimentation rate, even after the patient had apparently recovered. Cardiac enlargement, with subsequent reduction in size demonstrable by x-ray, was observed in three instances, and in these same patients pleural and pulmonary abnormalities were also present. Recurrences developed in three patients. Bradycardia existed in two and auricular fibrillation in one. Profuse perspiration was a common complaint. The characteristic pericardial friction rub considered as associated with 60 to 75% of all cases of acute nonspecific pericarditis was conspicuous by its absence in four of this group.

The close resemblance of the clinical picture in three of the above patients to that of acute myocardial infarction led to the use of anticoagulants early in the course of the disease, but this therapy was interrupted as soon as the diagnosis of pericarditis became apparent. A rheumatic etiology was suspected at the outset in cases 1 and 5 because of their age, arthralgia and elevated antistreptolysin titer. The electrocardiograms for the entire group

were consistent with what may be observed in pericarditis. Although initially several were interpreted as consistent with myocardial infarction, particularly cases 2, 3 and 4, nevertheless we felt that the clinical picture as well as the serial changes and the return of the abnormal alterations to their original status favored the diagnosis of acute nonspecific pericarditis. The presence of acute myocardial infarction could not be absolutely excluded.

The terms acute nonspecific pericarditis, acute idiopathic pericarditis, acute benign nonspecific pericarditis, acute pericarditis of the benign type, acute pericarditis of undetermined cause, acute pericarditis of the nonsuppurative type, acute relapsing pericarditis, fugitive pericarditis and cryptic pericarditis are all synonyms for the same disease. It is a benign condition of acute nature, having frequent recurrences and usually ending in complete recovery. It affects males more frequently than females, in a ratio of 3:1, and although no age group is exempt, it is more often observed in the second to fourth decades.

Although the exact etiology is as yet obscure, numerous causes have been suggested.² There are those who believe that since over 50% of cases reported give a history of previous upper respiratory illness, a virus may be responsible.^{13, 14, 15} The allergic theory also has its supporters,^{14, 18} who contend that the body becomes sensitized to a previously invading organism or its toxic products, and that the antigen-antibody reaction thus initiated results in pericarditis. Others feel that its close resemblance to rheumatic fever would speak for a similar genesis.^{3, 20} This latter concept is gaining more adherents at present because of the emergence, following mitral commissurotomy, of a febrile syndrome having many features in common with acute idiopathic pericarditis.¹⁹ Dressler ²⁰ believes that since the cause of this clinical picture is rheumatic reactivation, idiopathic pericarditis must be due to the same mechanism.

In the very early stages of this disease some individuals may appear quite ill, and occasionally the condition may even be ushered in by peripheral collapse with cardiac arrhythmia, thus making it difficult to differentiate it from a more serious cardiac disorder, such as myocardial infarction. In a short time, however, the patients rally and take on the appearance of benignity, despite the laboratory and electrocardiographic abnormalities suggesting serious involvement.

The outstanding complaint that leads the patient to seek medical attention is pain in the chest. This is variously described as a heaviness, a tightness, or a knifelike or constricting pain characteristically aggravated by bodily motion and respiration and radiating upward towards the neck and shoulders and downward to either hand or to the abdomen. Because of its nature and distribution it may lead to a mistaken diagnosis of pleurisy, pneumothorax, an acute abdominal emergency, or acute coronary occlusion. In fact, the latter condition and nonspecific pericarditis are often so extremely difficult to differentiate on the basis of pain alone that only time and careful attention

to the patient's clinical progress and the laboratory data can clarify the situation.

Fever is almost always present at some stage of the disease, and may vary from the low-grade variety to one of considerable height. Profuse

perspiration is commonly observed.

The presence of a pericardial friction rub is considered by some to be essential for the diagnosis. The literature indicates that it is present in from one-half to three fourths of the patients. It need not always be audible, however, since it may be present for only a very brief period, or localized to such a very small area in the chest that it may be easily overlooked. Not infrequently it is so evanescent as to defy detection. It is a very helpful sign when audible, but if absent, the diagnoses must be based on other evidence. Although it was not recognized in four of our group, we none-theless adhered to our diagnosis of acute idiopathic pericarditis, which ultimately proved to be correct.

Cardiac enlargement is frequently noted in this disease and may be due either to an accumulation of fluid within the pericardial sac or to dilatation of the heart. As a result of such involvement, dyspnea and orthopnea are apt to develop. These symptoms often improve spontaneously as the infection subsides, but on rare occasions pericardial paracentesis is necessary to obtain relief. Characteristically, the size of the heart returns to normal with the retrogression of the disease, and this is best portrayed by repeated

x-ray examinations.

Pleural involvement and lung infiltrations are seen in about 50% of cases of pericarditis of the nonspecific type, and for some unknown reason the left lung is the more frequent site.^{5, 6} These are reversible, though they sometimes persist after the patient has apparently recovered.

Leukocytosis of the polymorphonuclear variety and marked elevation of the sedimentation rate appear early in the course of the disease. The former returns to a normal level as soon as the acute infectious state subsides, but the latter persists for a long time, even in the face of complete recovery. The antistreptolysin titer may be elevated in this condition, but since this determination merely indicates a previous streptococcal infection, it is of no specific value as an aid in diagnosis. Recently the transaminase level in the blood has been shown to be normal in pericarditis but considerably elevated in myocardial infarction, and this may prove to be an extremely useful laboratory aid in the differentiation of the two disorders.

The most important clue in the recognition of nonspecific pericarditis is the serial electrocardiographic changes observed during its course. In the beginning there is an elevation of the ST segment in one or more leads, and within a period of a few days to a week this elevation returns to the normal iso-electric level. Shortly thereafter there is an inversion of the T wave in several of the limb and unipolar limb and chest leads. A discordant relation of the T waves in Leads 1 and 3 is infrequent but possible,

while a significant Q wave is almost never present except in V₁ and V₂. Within a period of six weeks to three months or more the T waves return to the upright position. Although similar alterations can be seen in myocardial infarction, such extensive changes would have to be interpreted as indicative of both anterior and posterior wall involvement. In such instances patients appear far more ill, and rarely if ever do their electrocardiograms return to normal in so short a time. In myocardial infarction one invariably finds a discordant relation between T₁ and T₃, and Q waves are almost always present.

There is no definitive therapy for idiopathic pericarditis, although the literature contains reports on the use of various antibiotics 9, 10, 11 and ACTH 12 in its treatment. Since all patients recover completely without sequelae, it is difficult to make an accurate assessment of any specific remedy. Rabiner and his co-workers recently reported a case of contrictive pericarditis that is alleged to have followed acute benign pericarditis, but proof for this was lacking. 17 We have employed symptomatic therapy with antibiotics where indicated, particularly when pulmonary signs became manifest, and our results were in no way different from what other observers

have reported with any specific agent.

Thus it appears that, although the diagnosis of acute idiopathic pericarditis may be difficult at times, it can and should be made on the basis of the above mentioned clinical criteria, as well as of the serial electrocardiographic changes so characteristic of the condition. Failure to detect a pericardial friction rub would not necessarily invalidate such a diagnosis, since at times this sign may be missed. A familiarity with this clinical syndrome will be most rewarding, both in its own recognition and in its differentiation from acute myocardial infarction, which it so closely resembles.

SUMMARIO IN INTERLINGUA

Viste le stricte similitude de acute pericarditis benigne con acute occlusion coronari con infarcimento myocardial, il es importantissime differentiar le duo conditiones, proque le prognose e le tractamento es nettemente contrari. Le prime del duo conditiones resulta usualmente in complete restablimento sin sequellas, e le uso in illo del anticoagulantes que es costumari pro le secunde pote provar se disastrose.

Le diagnose de acute pericarditis nonspecific es suggerite per le triade de symptomas de (1) dolores precordial aggravate per tusse e movimentos respiratori e corporee, (2) signos de infection, e (3) un frottamento pericardial. Iste diagnose es confirmate per alterationes electrocardiographic in serie. Un frottamento pericardial que appare precocemente e persiste durante plure dies debe esser considerate como un signo importante, sed illo non es presente o detegibile in omne casos. Su complete absentia in quatro del cinque casos hic presentate prova que le condition pote exister sin illo.

Le causas possibile include un virus, allergia, e le factores responsabile pro febre rheumatic. Le molestia principal, dolores thoracic, indicarea pleuritis, pneumothorace, acute disordine abdominal, o occlusion coronari. Allargamento cardiac, debite al accumulation de fluido in le sacco pericardial o al dilatation del fibras del musculo cardiac, pote supervenir. Le mesmo es ver pro implicationes pleural e

infiltration pulmonar. Ambe iste conditiones es completemente revertibile. Leucocytosis e un accelerate sedimentation se observa precocemente. Le prime de iste conditiones regrede con le infection acute, sed le secunde perdura le stadio active del morbo. Le plus importante indicio in le detection de pericarditis nonspecific es le alterationes del electrocardiogrammas in serie. Istos es plus diffuse que in infarcimento myocardial, in despecto del aere de ben-esser del patiente e le retorno a formas normal in un breve periodo de tempore. Recentemente on ha demonstrate que patientes con documentate episodios de infarcimento myocardial exhibi stigmas electrocardiographic ancora un anno plus tarde.

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CASE REPORTS

BILATERAL RENAL VEIN THROMBOSIS AND THE NEPHROTIC SYNDROME*

By Benjamin M. Kaplan, M.D., Julius S. Newman, M.D., Ervin Kaplan, M.D., Lyle A. Baker, M.D., F.A.C.P., and John M. Lee, M.D., *Hine, Illinois*

Gradual thrombotic occlusion of the renal veins may be manifested by the nephrotic syndrome.¹⁻⁹ The entity is characterized by anasarca, proteinuria, hypoproteinemia and hyperlipemia in a patient who usually has overt evidence of thrombotic phenomena. At autopsy the renal veins are occluded by premortem thrombi, and the kidneys are moderately enlarged, showing interstitial

edema and fibrosis and tubular changes.

Thrombosis of the renal veins was reviewed by Abeshous 5 in 1945. In the "primary type," usually seen during infancy, extrinsic factors do not give rise to the thromboses. The thrombotic process is initiated in the renal vein or the intrarenal tributaries. Clinically this entity is typified by the sudden development of a palpable abdominal mass and hematuria in an infant with an ileocolitis, sepsis and dehydration. In such a patient, nephrectomy has been lifesaving.10 In the "secondary type" the renal vein thrombosis is a direct extension from thrombi in the inferior vena cava, or such collateral branches of the main renal vein as the spermatic, ovarian, adrenal, ureteral or lumbar veins. Suppuration may or may not be present. Clinically, the "secondary type" is characterized by localized pain, with tenderness over the kidney, enlargement of the kidney, hematuria, albuminuria, oliguria or anuria, fever, leukocytosis gastrointestinal symptoms and vascular collapse. Very often there is accompanying thrombophlebitis of the lower extremities and pelvis. An associated disease may be present, such as thromboangiitis obliterans, periarteritis nodosa or amyloidosis.

There is a paucity of literature concerning bilateral renal vein thrombosis associated with the nephrotic syndrome. Derow 6 described a case of a 15 year old boy with recurrent thrombophlebitis of the lower extremities who developed the nephrotic syndrome one year prior to death. Thrombophlebitis of the external jugular and subclavian veins was also evident in the course of the disease. The patient's urine showed a massive amount of albumin, a few white blood cells and red blood cells, and double refractile bodies. Hypercholesteremia and hypoproteinemia with a reversal of the A/G ratio were present. Autopsy

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revealed old recanalized and fresh fibrin thrombi in the inferior vena cava, paratracheal, portal, splenic, renal and mesenteric veins. Microscopic examination of the kidneys revealed no abnormality of the glomerular epithelium, endothelium or basement membrane. The tubules showed slight cloudy swelling and double refractile bodies.

Fishberg 4 described a patient with renal vein thrombosis and nephrotic syndrome who during life had a migrating phlebitis with thrombosis of the inferior vena cava. Subsequently the patient developed the classic picture of the nephrotic syndrome, with anasarca, proteinuria, hypoproteinemia and lipemia. He died two years later following erysipelas, and at necropsy canalized thromboses of the inferior vena cava and renal veins as well as congestion and lipoidosis of the kidneys were noted.

Bell ² presented a case of a 43 year old male who, following an attack of acute hydrogen cyanide poisoning, developed heavy albuminuria and edema of the lower extremities. Intravenous pyelography showed no excretion by either kidney. The patient's blood urea nitrogen and blood pressure first increased but later decreased. At autopsy the inferior vena cava and right renal vein were occluded by thrombi and the left renal vein was nearly closed. Microscopic examination disclosed tubular atrophy throughout the cortices of both kidneys.

Allen ³ showed photomicrographs of the minor changes in the renal parenchyma following long-standing thrombosis of the main renal veins with the associated clinical syndrome simulating lipoid nephrosis. Scattered interstitial fibrosis, tubular degeneration and protein casts were noted.

Miller and co-workers ⁷ have reviewed the literature of this entity and present an additional case. Their patient developed a nephrotic syndrome following an appendectomy with the typical clinical findings of hypoproteinemia, albuminuria, anasarca and hypercholesteremia. Death followed in three months. Prior to death the patient experienced a severe cellulitis of the abdomen, thrombophlebitis of the lower extremities, a marked anemia and a pericardial friction rub. Necropsy disclosed polyarteritis nodosa involving the testes, pancreas and liver, with bilateral thrombosis of the renal veins, multiple thromboses of the pulmonary arteries and arterioles, and severe focal myocarditis.

Blainey and co-workers ⁸ presented one proved case of renal vein thrombosis with the nephrotic syndrome, and one other case in which the diagnosis was suspected but not proved, as an autopsy was not performed. The first individual was a 72 year old male who presented himself with bilateral edema of the lower extremities following a fall. Blood pressure was recorded as 190/100 mm. of Hg. Three to four months later he developed proteinuria and an increase in the edema, followed by hypoalbuminemia. The patient died in uremia and at necropsy showed thromboses of the renal veins, inferior vena cava, and iliac and femoral veins, in addition to a pulmonary embolus and multiple pulmonary infarcts. Histologically, the most significant findings in the kidney were tubular fatty changes.

Recently we have had the opportunity of extensively studying a patient with such a syndrome. Many clinical and laboratory observations are recorded, which help to define more accurately this seldom recognized entity. We feel that reporting this additional case will call further attention to this entity, adding

impetus to the establishment of the premortem diagnosis with its therapeutic implications.

CASE REPORT

First Hospital Admission: A 29 year old white male freight mover was first admitted to the Veterans Administration Hospital, Hines, Illinois, on May 19, 1950, complaining of shortness of breath and mild chest pain of four weeks' duration. At physical examination fine, moist, crepitant râles were heard throughout the lung fields. Blood pressure was 120/100 mm. of Hg. Pulse was 80, equal and regular. The point of maximal impulse of the heart was in the sixth interspace, 2 cm. to the left of the anterior axillary line. There was a soft, blowing, Grade II systolic murmur at the apex. P2 equaled A2. The liver was not felt, and there was no pretibial edema. Chest x-ray showed increased bronchovascular markings indicative of pulmonary congestion. The transverse diameter of the heart disclosed a 20% enlargement. The electrocardiogram contained nonspecific abnormalities. Urinalysis showed a 2 plus albuminuria. Red blood count was 3,920,000, with 11 gm. of hemoglobin. The nonprotein nitrogen was 33 mg.%. Treatment consisted of bed-rest, digitoxin, Thiomerin and ammonium chloride. The patient, after slow recovery, was discharged much improved 70 days following admission. In the ensuing six months he was seen twice for follow-up examination. He remained in good condition.

Second Hospital Admission: The patient was admitted June 15, 1951, for a persistent leukocytosis, although no symptoms were present. The electrocardiogram was within normal limits, and the chest x-ray showed the heart to be normal in size. An I¹³¹ uptake was reported as 32% in 24 hours. The patient had been off digitalis since June 1, 1951, and redigitalization was not considered necessary at this time.

Third Hospital Admission: The patient was re-admitted to the hospital on November 16, 1951, with the chief complaints of a nonproductive cough, dyspnea, orthopnea, palpitation, chills and sweating. Physical examination revealed a blood pressure of 120/80 mm. of Hg, a persistent tachycardia (100 to 120), occasional crepitant râles in both bases, moderate cardiac enlargement, a blowing systolic murmur at the apex, and slight pitting edema of the lower extremities. The white blood count was 12,000, with an increase in neutrophils. Urinalysis showed a trace of albumin. Blood urea nitrogen and fasting blood sugar were within normal limits. Several blood cultures were negative. The electrocardiogram showed a sinus tachycardia with evidence of left ventricular strain and digitalis effect. Treatment consisted of bed-rest, low salt diet and redigitalization. The patient left the hospital against medical advice on December 12, 1951, somewhat improved.

Fourth Hospital Admission: The patient returned to the hospital on April 2, 1952, complaining of a productive cough, shortness of breath, precordial pain and a 14 pound weight loss. Physical examination disclosed a temperature of 100° F; pulse, 120; blood pressure, 140/100 mm. of Hg. He exhibited mild congestive failure, which responded to digitoxin and moderate salt restriction.

Fifth Hospital Admission: The patient's next hospital admission was on November 4, 1952, at which time he complained of chills, sweats, fever, shortness of breath and chest pain. Physical examination was essentially the same as on the previous admission. His heart was increased in size from the previous admission. The electrocardiogram disclosed a sinus tachycardia, with left ventricular strain and digitalis effect. Red blood count, hemoglobin, serum sodium and serum potassium were within normal limits. The white blood count was 14,000. The nonprotein nitrogen was 42 mg.% and fasting blood sugar was 122 mg.%. The serum cholesterol was 222 mg.%. Several blood cultures were negative. The patient was again treated with a low salt diet, salicylates, digitalis and Thiomerin, in addition to penicillin. He responded well and was discharged in good condition.

Sixth and Seventh Hospital Admissions: On January 15, 1953, and on March 25, 1953, the patient was admitted for congestive heart failure. On both occasions he responded well to therapy. At that time the laboratory data showed a trace of albumin in the urine and a specific gravity of 1.020. Total serum protein was 6.9 gm.%, with an albumin of 3.4 gm.% and globulin of 3.5 gm.%. An upper gastro-intestinal series and gall-bladder series were normal.

Table 1
Serum Lipid Levels in a Case of Renal Vein Thrombosis with Nephrosis

Date	Total Plasma Cholesterol (mg.%)	Plasma Lipid Phosphorus (mg.%)	C/P Ratio	Total Plasma Lipids (mg.%)
1/9/54 1/12/54	896 783	35.9 38.7	25.0	3360

Eighth Hospital Admission: The patient entered the hospital for the last time on July 7, 1953. The chief complaint at that time was the sudden onset of inability to use his left arm and leg. He also had difficulty in speaking and was confused. Physical examination revealed a dyspneic, aphasic, confused individual. His eye grounds showed a slight amount of AV nicking. There were dullness and decreased fremitus over the right base of his lung, and moist râles at the left base. His pulse was 110. Blood pressure on the right arm was 88/75 mm. of Hg, while in the left arm it was 115/90 mm. of Hg. A Grade III systolic murmur was noted at the apex, and a protodiastolic gallop rhythm was present. The left heart border was enlarged to the

Table 2
Electrophoretic Fractionation of Plasma Protein in a Case of Renal Vein Thrombosis with Nephrosis

	Renal Vein Thrombosis with Nephrosis *		Normal †
	Mg. %	Area %	Area %
Total protein	4.01	100	
Albumin	0.54	13.5	54.40
Alpha ₁ globulin	0.28	7.0	4.96
Alpha ₂ globulin	0.34	8.5	12.29
Beta globulin	1.95	48.5	9.42
Fibrinogen	0.36	9.0	6.82
Gamma globulin	0.54	13.5	12.36

* Determinations were made on the Klett electrophoresis apparatus.

† Normal values were based on average value for 18 normal individuals.

Determinations through courtesy of the Medical Research Service, Veterans Administration Hospital, Hines, Illinois.

left anterior axillary line in the sixth interspace. There was a 2 plus pitting pretibial edema. Neurologic examination revealed left hemiparesis, with hypoactive deep tendon reflexes and a positive Babinski on the left side. The patient responded slowly to the routine management for congestive failure. Likewise, the hemiparesis gradually disappeared and the aphasia became less outstanding. The abdominal discomfort which he had had on previous admissions recurred intermittently. Four months prior to his death it was first observed that the patient's face was puffy and the skin pale. Edema of the ankles became apparent, and albuminuria was marked. Subsequently



Fig. 1. Percutaneous renal biopsy in bilateral renal vein thrombosis with nephrotic syndrome. See text.

anasarca and the classic picture of the nephrotic syndrome developed. The blood lipids increased markedly, the plasma cholesterol rising to 783 mg.% and 1,200 mg.% on separate occasions. A more complete study of the lipids was made (table 1). Electrophoretic fractionation of the plasma proteins was done (table 2). With the development of the nephrotic syndrome the patient no longer manifested congestive failure. However, he continued to run a downhill course, with increasing pallor and anasarca. The specific gravity of the urine varied between 1.004 and 1.020, and contained varying numbers of red and white blood cells and occasional hyaline and granular casts. Culture of the urine at various times showed Bacillus coli, Streptococcus faecalis and Aerobacter aerogenes. On two occasions the urine showed a trace of sugar; however, repeated fasting blood sugars were within normal limits. The patient's nonprotein nitrogen rose from 21.2 mg.% to 69.4 mg.% prior to death. The phenolsulfonphthalein excretion was 23% in four hours. An intravenous pyelogram did not visualize the renal pelves. A subsequent retrograde pyelogram was normal. A percutaneous kidney biopsy was performed with the Vim-Silverman needle. The histologic sections contained six glomeruli and little medulla. Moderate dilation of the tubules was noted; they contained hyaline, protein-like substance, and some contained polymorphonuclear leukocytes and lymphocytes. The glomeruli showed minimal thickening of the basement membrane. The interstitial tissue was mildly fibrosed and contained a few scattered chronic inflammatory cells (figure 1). Other laboratory procedures were performed: An L.E. cell preparation was negative. I181 uptake was 40% in 24 hours. Serum alkaline phosphatase was 22.8 mg.%; calcium, 7.1 mg.%; phosphorus, 3.8 mg.%. Frequent serum sodium and potassium determinations were within normal limits, except on one occasion prior to death, when a potassium value of 2.7 mg.% was recorded. At this time the patient complained of extreme lethargy and weakness, which disappeared upon administration of potassium. An upper gastrointestinal series disclosed "pylorus spasm." Stools for ova and parasites were negative. A biopsy of the gastrocnemius muscle was negative for periarteritis nodosa. Urine examinations disclosed amino-aciduria by paper chromatography; however, the exact amino acids were not determined. A Sulkowitch's test was positive late in the patient's course. The quantitative urine phosphorus was 0.2 gm., while the albumin was 1.84 gm. per 24 hours. A bone survey was essentially normal. Chest x-ray disclosed borderline cardiac enlargement. Many electrocardiograms were taken on this patient which showed T wave and ST segment changes; the primary interpretation was left ventricular strain with digitalis effect.

During the patient's final admission all efforts to promote diuresis were unsuccessful. At various times during this period the patient received mercurial diuretics, digitalis, testosterone, serum albumin and ACTH. Several transfusions were given to treat the patient's anemia. He died on February 23, 1954, following a massive gastrointestinal hemorrhage. At no time during his illness was there clinical evi-

dence of thrombophlebitis of the lower or upper extremities.

Autopsy Findings: At necropsy the body was pale and edematous throughout. The right and left pleural spaces contained 1,000 and 500 c.c. of gray, cloudy fluid, respectively. Many fibrous adhesions of the pleural spaces were noted, especially on the diaphragmatic surface. The right lung weighed 590 gm., the left, 570 gm. The cut surfaces of both lungs were dark, and fluid readily exuded upon section. An abscess 3 cm. in diameter containing thick greenish pus was present in the lower lobe of the right lung. Organized thrombi were noted in the main branches of the right and left pulmonary arteries. The pericardial cavity was obliterated by fibrous adhesions. The heart weighed 390 gm.; the myocardium was pale and flabby. The coronary vessels were smooth, elastic and patent. The mitral and aortic valves were slightly thickened. The ascending and descending aorta showed a moderate amount of atherosclerosis. The peritoneal cavity contained 2,000 c.c. of a milky fluid. The

liver weighed 2,070 gm., was a pale, yellowish brown, and showed a fine granularity on cut surface. Each kidney weighed 220 gm.; the capsules stripped with ease, leaving a yellowish surface. The cut surfaces of both kidneys appeared pale, and the cortices and medullae were indistinct. Both renal veins were completely occluded

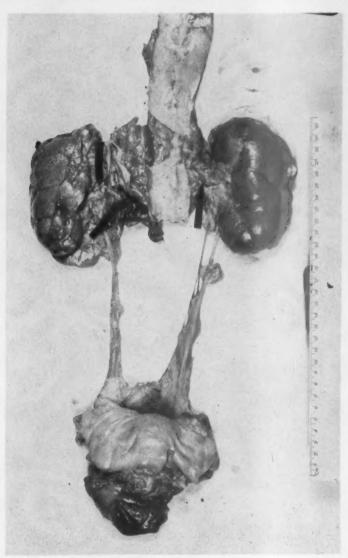


Fig. 2. Gross specimen, bilateral renal vein thrombosis and thrombosis of inferior vena cava. See text.

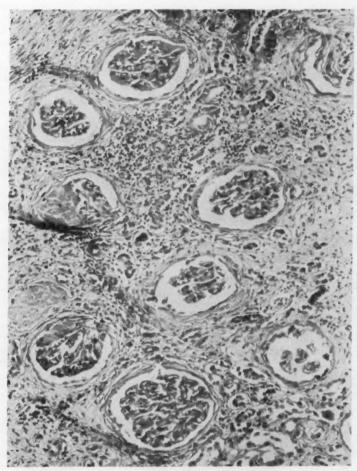


Fig. 3. Renal histopathology at autopsy in bilateral renal vein thrombosis with nephrotic syndrome. See text.

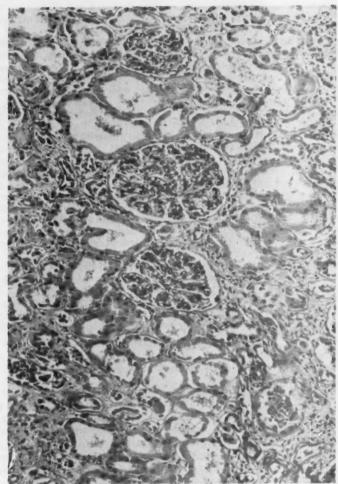


Fig. 4. Renal histopathology at autopsy in bilateral renal vein thrombosis with nephrotic syndrome. See text.

by antemortem thrombi. These thrombi were continuous with a thrombus in the inferior vena cava, which occluded this vessel from the junction of the common iliac veins upward to the liver (figure 2). In the first and second portions of the duodenum two superficial linear ulcers were found. In addition, a large ulcer measuring 2 by 1 cm. in diameter was present in the second portion of the duodenum. The base of this ulcer was adherent to the head of the pancreas. At one pole of the spleen

there was a soft yellow area 4.0 cm. in diameter.

Microscopic: Microscopic examination of the heart disclosed edema of the interstitial tissue and some replacement of myocardial fibers by fibrous tissue. The lungs showed small area of atelectasis. In addition, there was marked congestion throughout. In one section there was infiltration with inflammatory cells typical of lobar pneumonia; in another area there was microscopic evidence of the lung abscess. Many of the small vessels of the lungs were completely occluded by fresh and organized thrombi. The sinusoids of the liver were slightly widened, and the reticuloendothelial cells in the sinusoidal spaces were hypertrophied. There was heavy pigmentation with hemosiderin throughout the liver. The glomeruli of the kidneys were edematous, almost completely filling the space of Bowman. Some glomeruli showed evidence of fibrosis. In many areas there was marked interstitial fibrosis and infiltration with chronic inflammatory cells. Many tubules contained precipitated material, cellular debris and polymorphonuclear leukocytes (figures 3 and 4). In a few sections there was evidence of recent infarction of the kidney. The larger arteries of the kidneys showed marked sclerosis with intimal thickening. Both adrenal glands showed thrombi in the medulla. Microsection of the vena cava and renal veins showed old and recent thrombi. Some of the thrombi were calcified; calcification was noted in the wall of the veins as well. The brain disclosed thrombosis of the smaller arteries, accompanied by cerebral softening.

Anatomic Diagnosis: (1) Thrombosis, old and recent, of the vena cava and both renal veins with organization and calcification. (2) Pyelonephritis. (3) Pulmonary thrombi, old and recent. (4) Lobar type pneumonitis. (5) Lung abscess. (6) Pulmonary congestion, edema and atelectasis. (7) Duodenal ulcer, recent, penetration. (8) Myocardial edema and fibrosis. (9) Multiple small recent thrombi of the adrenal medulla. (10) Cerebral arteriosclerosis with thromboses of small cerebral

arteries and cerebral softening.

DISCUSSION

From a clinical standpoint this patient offered a diagnostic challenge from the onset of his illness. It was originally felt that he had a nonspecific myocarditis with congestive heart failure. There were no definite findings to suggest primary renal disease early in his illness. With the development of the nephrotic syndrome, the manifestations of myocarditis and congestive heart failure disappeared. Exactly what was responsible for this course of events is not known; however, one might postulate that the pooling of fluid in the tissues acted as a homeostatic mechanism to decrease both the total intravascular volume and the venous return to the heart. There have been reports in the literature of improvement of congestive heart failure following ligation of the inferior vena cava, which, of course, took place spontaneously in this case. The neurologic findings were secondary to cerebral thrombosis, with resulting cerebral softening. The existence of extrarenal thrombosis in this syndrome has been previously noted. 4, 6, 7, 8 Another unusual feature of this case was the recurrent diffuse abdominal pain. Patients with idiopathic hyperlipemia may have severe ab-

dominal pain. However, in addition to the hyperlipemia, this man had several duodenal ulcers which could have accounted for his abdominal distress. The patient's gastrointestinal symptomatology did not increase following the use of ACTH. It is possible, however, that the latter drug could have played a part in increasing the size of the duodenal ulcers that were so apparent at autopsy.

The patient's total serum lipids, phospholipids and cholesterol parallel the determinations noted in the nephrotic syndrome of other causes 12 (table 1).

As far as can be ascertained, there is no report in the literature in which ligation of the renal veins in animals has produced a clinical picture of the nephrotic syndrome or hyperlipemia. Rowntree ¹³ has shown, in animals, that partial obstruction of the inferior vena cava, proximal to the renal veins, or of the renal veins themselves, leads to a rise in pressure in the renal veins and to persistent proteinuria. Heyman and Clark ¹⁴ and Winkler and co-workers ¹⁵ have induced lipidemia in animals by bilateral adrenalectomy and ligation of the ureters. Lipidemia has been noted after nephrotoxic nephritis. ¹⁶

TABLE 3

Serum Lipoproteins in Milligrams per 100 ml. of Serum as Determined by Ultracentrifugation in a Case of Renal Vein Thrombosis with Nephrosis²⁴

	Normal (Males, Age 18-34)	Renal Vein Thrombosis with Nephrosis
$-S^* = 4$	153.7 ± 5.1	< 20
-S = 23	11.6 ± 1.1	150
-S = 30	200+	750
-S = 40 to 70	24.2 ± 1.8	550
-S > 70	36.7 ± 3.8	>800

* Negative sedimentation.

Determinations courtesy of the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.

Electrophoresis of this patient's serum protein disclosed a marked decrease of albumin with an increase of beta globulin (table 2). The alpha 2 globulin was not increased. The latter finding was the only inconsistency in comparing electrophoretic fractionation values, in this case with those seen in the nephrotic syndrome of other etiologies. The lipoproteins measured by ultracentrifugation disclosed the -S (negative sedimentation) abnormalities as described by Lewis and Page for the nephrotic syndrome 17 (table 3). In addition to an increase in the -S (>70) fraction, there was a definite increase in the -S (40–70), -S (30) and -S (23) fractions. The latter is probably related to the increase in beta globulin noted by electrophoresis.

Suspicion of an adult Fanconi's syndrome ¹⁸⁻²⁰ was aroused by a number of factors. Percutaneous renal biopsy disclosed dilated renal tubules with alterations in the tubular epithelium. The patient had an occasional episode of reducing substance in the urine, in addition to proteinuria. Paper chromatography disclosed an increased quantity of amino acids in the urine as compared with normal controls. However, Squire has shown that increased amino-aciduria may accompany nephrosis, especially if the patient is on a high protein diet.²¹ Clinical and laboratory evidence of hypokalemia was noted; the clinical episodes were alleviated following administration of potassium. The serum alkaline phosphatase was also elevated. Despite this information, subsequent

laboratory and clinical findings did not substantiate the impression of an adult Fanconi's syndrome.

The failure of the intravenous pyelogram to show excretion of the dye has been noted in previous reports.^{2, 6} Our finding of a normal retrograde pyelogram is in contrast to that reported by Melick and Vitt.²² Evidently distortion of the renal pelvis must be dependent on other factors than mere occlusion of the renal veins.

Percutaneous renal biopsy has been reported in patients with a nephrotic syndrome.^{23, 24} In our case the microscopic histology did not reveal engorgement of the glomeruli or smaller renal veins. Although this examination was not diagnostic of renal vein thrombosis, it did help rule out various entities considered in the premortem differential diagnosis. Such diseases as amyloidosis, periarteritis nodosa, lupus erythematosus and chronic glomerulonephritis had received diagnostic consideration.

Progressive histopathologic changes were most evident in comparing the biopsy sections with those obtained at autopsy three months later. The most significant change was the marked increase in interstitial fibrosis and inflammatory cell infiltration. The tubular dilatation decreased and the epithelial cells were less flattened. The glomeruli were markedly more engorged, and various degrees of glomerular fibrosis was noted post mortem (figures 1, 3 and 4).

Various observations should heighten the suspicion of bilateral renal vein thrombosis as an etiologic factor in the nephrotic syndrome: first, the development of the nephrotic syndrome in an adult with no previous history or findings of renal disease; second, the occurrence of nephrosis associated with any intravascular thrombotic or embolic phenomena, or unrelated disease which through stasis or inflammation may predispose to thrombosis; third, a progressive downhill course without the remissions common to nephrosis of other etiologies. As previously stated, percutaneous renal biopsy may rule out other etiologies of the nephrotic syndrome. Venography may be considered in establishing thrombosis of the inferior vena cava and renal veins. The diagnosis of renal vein thrombosis is of more than academic value, since with the use of anticoagulants and/or surgery the progression of the disease may be altered or, perhaps, even completely interrupted.

SUMMARY

- 1. The seventh case of bilateral renal vein thrombosis associated with the nephrotic syndrome is reported. The literature of this entity is reviewed in detail.
- 2. The outstanding clinical features of this case are described, and the laboratory findings, including the kidney biopsy, are emphasized.
- 3. A comparison of the histologic findings of the kidney biopsy and the histologic findings of the kidney at autopsy three months later is presented.
- 4. The diagnostic criteria of this syndrome are outlined, as formulated from a review of the cases in the literature and our case.
 - 5. The therapeutic possibilities are briefly discussed.

ACKNOWLEDGMENT

We are indebted to Dr. R. M. Kark and Dr. J. Lindberg for the kidney biopsy.

SUMMARIO IN INTERLINGUA

Occlusion thrombotic general del venas renal pote manifestar se per le syndrome nephrotic. Le entitate es characterisate per anasarca, proteinuria, hypoproteinemia, e hyperlipemia in un patiente usualmente con patente evidentia de phenomenos thrombotic. Al autopsia le venas renal es occludite per thrombos premortal, e le renes es moderatemente allargate e exhibi edema interstitial, fibrosis, e alterationes tubular. Es presentate un revista detaliate del litteratura relative a iste entitate. Nos presenta le septime caso de iste typo de syndrome e describe le prominente constatationes clinic e laboratorial, incluse constatationes bioptic. Un comparation del histologia del biopsia renal con le constatationes histologic al autopsia tres menses plus tarde revelava un marcate augmento del fibrosis interstitial e un extense infiltration per chronic cellulas inflammatori.

Varie observationes pote servir a reinfortiar le suspicion de thrombosis bilateral del venas renal como factor etiologic in le syndrome nephrotic: Primo, le disveloppamento del syndrome nephrotic in un adulto sin previe historia o constatationes de morbo renal; secundo, le occurrentia de nephrosis associate con non importa qual genere de intravascular phenomenos thrombotic o embolic o con un morbo independente que tende (per stase o per inflammation) a effectuar un diathese thrombotic; tertio, un progressive deterioration sin le remissiones que es commun in nephrosis de altere etiologias. Le percutanee biopsia renal pote servir a eliminar altere etiologias del syndrome nephrotic.

Venographia pote esser considerate como adjuta in establir le presentia de thrombosis del vena cave inferior e del venas renal. Le diagnose de thrombosis del venas renal es de valor plus que purmente academic, proque le uso de anticoagulantes e/o de methodos chirurgic pote resultar in le alteration del progresso del morbo o forsan mesmo in su complete interruption.

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VARICELLA PNEUMONIA: CASE REPORT *

By RAY G. COWLEY, Lt. Colonel (MC), WILLIAM E. CREW, Captain (MC), and GERARD R. HASSETT, 1st Lieutenant (MC)

ONE of the rare and serious complications of varicella is diffuse involvement of the pulmonary parenchyma by the varicella virus. Fifteen cases developing this complication have been reported in the American literature to date.1-12 It is the purpose of this article to present another case of "primary varicella pneumonia" occurring in an adult.

CASE REPORT

A 33 year old Hawaiian male was admitted to a U. S. Army Hospital on November 22, 1954. Approximately five weeks prior to admission his six year old son had

^{*} Received for publication April 19, 1955. From the 11th Field Hospital, Germany. Requests for reprints should be addressed to Ray G. Cowley, Lt. Colonel (MC), Post Office Box 115, William Beaumont Army Hospital, El Paso, Texas.

developed typical varicella, having been exposed in school during a minor varicella epidemic. Two weeks prior to admission two daughters developed varicella. The course of the disease in his children was typical and uncomplicated.

Three days prior to admission the patient developed chilly sensations, malaise, fever and pain behind the eyes. On the second day of illness his temperature was found to be 100° F., and he was treated as an out-patient with Aureomycin, 250 mg. every six hours for one 24 hour period. Fever, malaise and chilly sensations continued, and on the third day of illness small vesicles were noted on the chest and forehead. The patient was hospitalized on the third day of illness for the purpose of isolation only. The course of the patient's illness prior to hospitalization was uncomplicated. No respiratory symptoms were noted.

Past History: The patient was a native of Honolulu, Hawaii, and had resided there until adulthood. He had been stationed in Western Germany for 29 months prior to the onset of the present illness. His present occupation was that of a cook. Childhood diseases included "red measles," "pink eye" and mumps. He had no history of chickenpox. A left herniorrhaphy had been performed when he was 6. Past hospitalizations: 1947 for peptic ulcer; 1953 for nonspecific urethritis; 1953 for pharyngitis. Recovery in all instances was uneventful, with no recurrences. Routine immunization (March, 1954) included smallpox with a vaccinoid reaction. Influenza vaccine, I c.c., had been given four days prior to the onset of the present illness, with no local or systemic reaction noted.

Physical Examination: Temperature on admission, 98.6° F.; pulse, 84; respirations, 20. This patient was a well developed male, not acutely ill. A moderately extensive, typical varicella eruption in various stages of development was present on the scalp, face, neck, trunk and proximal extremities. Several varicella lesions were present in the pharynx and on the soft palate. The remainder of the physical examination was within normal limits.

Laboratory Data on admission: White blood cells, 4,400, with 1% juveniles, 38% bands, 16% segmented neutrophils, 35% lymphocytes, 2% monocytes, 8% eosinophils. Hemoglobin, 16.7 gm. Sedimentation rate, 9 mm./hr. Cardiolipin, negative. Chest x-ray, normal (figure 1).

Hospital Course: The patient was placed in isolation and given symptomatic treatment consisting of local calamine lotion with 1% phenol, and oral Pyribenzamine, 50 mg. four times a day. Five hours after admission a 20 minutes shaking chill occurred, following which a temperature of 102.4° F. and a pulse rate of 100 were recorded. Symptomatic relief was obtained with aspirin, phenacetin and caffeine and oral codeine. During the second hospital day moderate sore throat and moderate, nonproductive cough developed. The temperature remained elevated near 101° F., and new cutaneous varicella lesions continued to appear. The lesions remained discrete and showed no evidence of secondary infection. Otherwise, during the first two hospital days the patient's course was uneventful and consistent with the diagnosis of uncomplicated varicella.

During the early morning of the third hospital day (sixth day of illness) the patient's temperature rose to 103° F., generalized chest pain developed, and cough became severe, paroxysmal and productive of diffusely blood-tinged, mucoid, tenacious sputum. During the next six to eight hours a marked feeling of weakness and fear of impending death developed. Breathing was rapid and shallow, and shortness of breath on minimal exertion was present. The patient was unable to think or concentrate clearly, and complete prostration rapidly developed. Physical examination at this point revealed the patient to be mildly cyanotic and dyspneic, with a respiratory rate of 36 and a pulse rate of 108. The peripheral pulse was strong and regular. He was very apprehensive and restless, and it was necessary for him to assume an upright position to avoid severe respiratory embarrassment. Examination of the heart was

normal. Examination of the lungs revealed fine, scattered, crepitant râles bilaterally. Neurologic examination was normal except for generalized, marked weakness, the patient being unable to sit upright unsupported. No change in the skin lesions was noted. Chest x-ray taken at this time revealed an extensive bilateral, nodular and interstitial-like infiltration (figure 2). On his being placed in an oxygen tent, im-

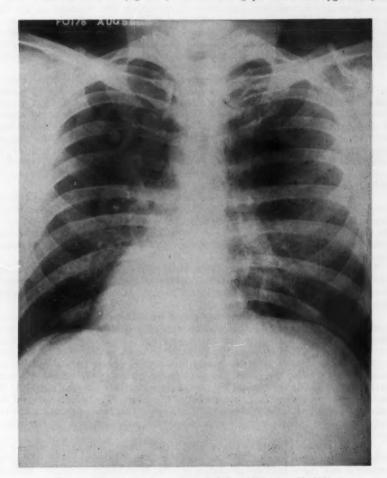


Fig. 1. Normal chest x-ray on admission, November 22, 1954.

provement in color, marked relief from the weakness and decrease in respiratory and pulse rate were noted. Throughout the remainder of the third hospital day his temperature remained elevated, with a peak of 103.8° F. His inability to ingest food or fluids necessitated the institution of intravenous fluid therapy, which was continued intermittently for 48 hours. Aureomycin, 250 mg. four times a day, was started as a prophylactic measure.

For a period of 48 hours the patient could not be removed from the oxygen tent without severe respiratory embarrassment developing. The severe paroxysmal, productive cough continued throughout this period. The sputum was not purulent at any time, and normal flora grew out on two cultures. Chest findings continued to show only scattered râles and minimal diminution of breath sound transmission. On the

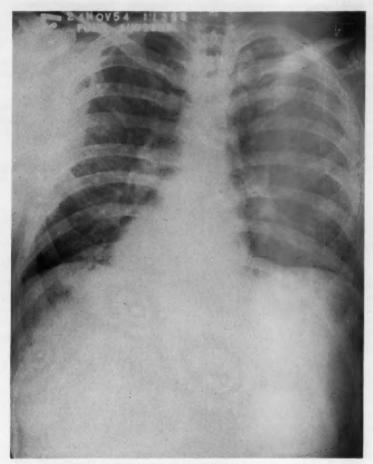


Fig. 2. Diffuse, nodular and interstitial-like infiltration throughout both lung fields on November 24, 1954.

fourth hospital day varicella lesions were noted to be scattered throughout the oral mucous membranes. The pharyngeal and palatal lesions had not changed, and no lesions were noted on the larynx.

Oxygen was not required after 48 hours (the eighth day of illness) because of rapidly improving respiratory function. The varicella skin lesions were at this point beginning to heal, and the temperature became normal and remained so. The vari-

cella lesions continued to run a typical course, with eschar formation, and no new ones developed. The cough abated gradually, with continued production of scanty, diffusely blood-tinged sputum for approximately two weeks, following which time the sputum production had become clear, mucoid and less than one-half oz. daily. Serial

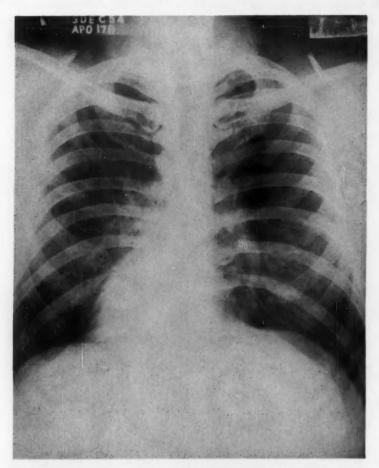


Fig. 3. There is complete resolution of the pneumonitis on December 13, 1954.

chest x-rays showed gradual clearing following the x-ray of November 25, 1954, with complete resolution of the diffuse pulmonary infiltration occurring by the twenty-fifth day of illness (figure 3).

Aureomycin, 250 mg. four times a day, was given for 10 days. Pyribenzamine, 50 mg. four times a day, was continued for five days. Serial white blood cell and differential counts during the entire illness showed no elevation of the white count above 8,000, and on the sixth day of illness a peak of 70% lymphocytosis was noted,

with rapid subsidence. At this point, several plasma cells were noted in the peripheral smear. The hemoglobin remained unchanged throughout.

Two 24-hour sputum specimens were collected in formalin fixative, a cell block was made and the sputum was studied in an attempt to find inclusion bodies of the type seen in varicella in the cellular elements of the sputum. Pathologic report on both sputa revealed a moderate predominance of squamous cells; the mononuclear cells seen failed to reveal any evidence of intranuclear or cystoplasmic inclusions resembling those seen in varicella. A biopsy of a skin lesion was performed on the tenth day of illness. It was felt that this was of no value diagnostically, being biopsied too late in the course of the disease. The clinical picture was typical of varicella, and the above pathologic procedures were carried out as possible adjunctive diagnostic procedures. Acute and convalescent agglutination studies for psittacosis, Q fever and primary atypical pneumonia were negative.

During the first week of illness three urine specimens contained from five to eight red blood cells per high power field, and one urine specimen contained a trace of albumin. Repeated urinalyses during convalescence were entirely normal. A blood culture taken on the third hospital day prior to the start of Aureomycin therapy was negative.

During a three month follow-up period the patient's chest x-ray remained normal, and the only symptom noted was a mild, nonproductive cough which persisted for approximately two months, with gradual subsidence.

DISCUSSION

The information available to the authors at the time of submission of this article indicates that this case of primary varicella pneumonia is the sixteenth to be reported in the American literature.

The first cases of this nature were reported by Waring, Neuberger and Geever in 1942.¹ The most recent articles pertaining to this subject by Hampton,¹² Rosecan, Baumgarten and Charles¹¹ and Saslaw, Prior and Wiseman¹⁰ contain literature reviews and summaries of the clinical and laboratory findings in all previously reported cases. The accumulated evidence strongly suggests that this complication of varicella, while very rare, is a distinct clinical entity, with characteristic findings, and that the agent producing the pulmonary changes is the varicella virus.

The symptomatology displayed by these cases as summarized is uniform, varying only in severity and in the type of cardiopulmonary complications arising therefrom, such as shock, congestive heart failure or azotemia. Concomitant involvement of visceral organs or the central nervous system by the varicella virus may complicate the picture. This complication should be considered when, in the course of varicella with typical cutaneous lesions, the following signs and symptoms occur: from the second to the sixth day of illness, severe cough, dyspnea, cyanosis and hemoptysis, with relatively normal white blood cell count and differential, nonspecific bacteriologic findings, a paucity of physical findings on examination of the chest, and a diffuse, nodular and interstitial-like infiltration in the chest roentgenogram.

There is no definite evidence that this condition responds to antibiotic therapy; and if death or severe cardiopulmonary complications do not develop, there is rapid recovery concomitant with onset of the healing phase of the cutaneous varicella lesions.

This case exhibited the described characteristic findings to a moderately severe degree with complete recovery. Agglutination studies for three other disease entities that could produce this picture were negative. There was no evidence that Aureomycin therapy was effective in altering the course of the disease process. It is probable that the only value of antibiotics in varicella infections is prophylaxis against secondary bacterial invaders. Because of the serious nature and the severity of this complication, the prophylactic use of antibiotics is not without merit.

SUMMARY

A case of primary varicella pneumonia in a 33 year old Hawaiian male is reported. The clinical and laboratory features of the disease process in this case are consistent with those described in previously published cases. The characteristic features of this rare and serious complication of varicella are discussed.

It is most probable that the varicella virus was the agent responsible for the pulmonary changes described. This case adds additional evidence that the usually benign varicella virus may occasionally produce serious pulmonary disease.

SUMMARIO IN INTERLINGUA

Post exposition a varicella, un masculo hawaian de 33 annos de etate disveloppava febre, malaise, e cutanee lesiones varicellic. Ille esseva hospitalisate con objectivo de isolation. Durante le prime cinque dies le morbo del patiente presentava le aspectos de un non complicate, moderatemente sever caso de varicella in un adulto. Le sexte die, le sequente symptomas e signos se disveloppava rapidemente: prostration, generalisate dolores thoracic, sever tusse paroxysmal con production de sputo a diffuse coloration sanguinose, cyanosis, dyspnea, e elevation additional del temperatura. A iste tempore le examine del thorace revelava un fin e disperse rhoncho crepitante bilateral, e le roentgenogramma del thorace monstrava un extense infiltration nodular bilateral de apparentia interstitial. Tres dies previemente un roentgenogramma thoracic habeva essite negative. Durante le 48 horas post le declaration del symptomas respiratori le patiente esseva seriemente malade, con sever tusse paroxysmal, sputo hemoptoic, sever embarasso respiratori post abduction ab le tenta a oxygeno, incapacitate de ingerer solidos o fluidos, e un elevation del temperatura usque a 42,1 C. Le tractamento durante le phase sever del maladia consisteva de fluidos intravenose, oxygeno, e Aureomycina. Le octave die del morbo, rapide meliorationes del symptomas respiratori e etiam del lesiones cutanee esseva notate. Le infiltration pulmonar regredeva gradualmente, e complete clarification esseva attingite 25 dies post le declaration del morbo. Le symptomas de hemoptysis e tusse persisteva durante duo septimanas. Le resanation esseva complete, sin sequelas detegibile. Le numeration leucocytic remaneva normal durante le integre curso del morbo. Le sexte die un lymphocytose de 70% esseva notate. Duo culturas de sputo resultava in normal floras. Durante le phases acute e convalescente, studios de agglutination pro febre de Queensland, psittacosis, e primari pneumonia atypic esseva negative. Studios cytologic del sputo, executate con duo specimens a fixation formalinic pro demonstrar corpores de inclusion del typo observate in varicella, remaneva negative. Il habeva nulle indication que le therapia a Aureomycina influentiava le curso del morbo.

Dece-cinque casos de iste complication de varicella esseva previemente reportate

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in le litteratura medical del Statos Unite. Le datos accumulate suggere que pneumonia a varicella, ben que rar, es un distincte entitate clinic que es producite per un invasion del parenchyma pulmonar per virus de varicella. Serie complicationes cardiopulmonar pote evenir, e exito mortal es possibile.

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CONGENITAL ANEURYSM OF THE NONCORONARY SINUS OF VALSALVA LEADING TO COMPLETE HEART BLOCK: CASE REPORT *

By Edmon B. Lee, M.D., Cranford, New Jersey, Oscar J. Krieger, M.D., Brooklyn, N. Y., and NORMAN K. LEE, M.D., Oakland, California

ANEURYSM of one of the aortic sinuses of Valsalva is a rare abnormality; about 45 cases have been reported. It has been attributed to congenital causes, lues, arteriosclerosis and subacute bacterial endocarditis. Taussig 1 stated that these aneurysms are most commonly due to lues. Of the seven cases reported by Venning,2 four were considered to be secondary to subacute bacterial endo-

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carditis. Morgan Jones and Langley,³ in their review of the subject, found that some cases considered congenital in origin had been incompletely studied from the standpoint of syphilis or cystic medial necrosis, and therefore had not been proved to be developmental in origin. The majority of case reports, however,

describe congenital lesions.

These primary lesions are believed to be due to congenital weakness of the elastic tissue in the wall of the heart at the base of the aorta.⁴ The right aortic sinus is most commonly involved. Due to its proximity to the membranous portion of the interventricular septum, right aortic sinus aneurysm leads to conduction disturbances ^{5, 6, 7} and to eventual rupture into the right ventricle or pulmonary artery, and occasionally into the right atrium.⁸ Aneurysms of the posterior or noncoronary aortic sinus are second in frequency, and tend to perforate into the right atrium. Aneurysms of the left aortic sinus are rare, and perforate into the left ventricle or pericardial sac. Eight cases of aneurysms of all three aortic sinuses have been reported. Associated congenital defects found with these abnormalities are: high ventricular septal defects, coarctation of the aorta ¹⁷ and bicuspid aortic valves.^{2, 9} The most commonly acquired complications are: rupture, coronary occlusion, heart block, subacute bacterial endocarditis and septic embolization. The overwhelming majority of reported cases had ruptured.

Aneurysms of the aortic sinuses are usually asymptomatic, or are associated only with those symptoms referable to the etiologic agent, until rupture or pressure of surrounding structures occurs. With rupture, there are sudden dyspnea, palpitations and collapse. A continuous machinery murmur is heard, with maximal intensity along the left sternal border in the third and fourth interspaces. There is usually rapid progression leading to death. The longest reported survival after rupture is nine years. When there is pressure on or infiltration into the conducting fibers, various phases of heart block and arrhythmias may occur. The condition is rarely diagnosed ante mortem. Maynard and Thompson of and Venning both correctly diagnosed a case following rupture. Falholt and Thomsen diagnosed an unruptured case ante mortem by means of aortography. Dubilier, Taylor and Steinberg treported aneurysmal dilatation of all aortic sinuses in three cases of coarctation of the aorta. Steinberg and Geller reported aneurysmal dilatation of aortic sinuses in arachnodactyly.

The majority of cases reported died of congestive heart failure, usually following sudden rupture into the right heart, with production of a massive left-to-right shunt. Other causes of death have been coronary occlusion due to pressure on one of the coronary orifices, overwhelming subacute bacterial endocarditis and cardiac tamponade. Heart block with Stokes-Adams seizures is a

rare cause of death.

CASE REPORT

The patient, a 32 year old Negro dyesetter, was admitted to the Brooklyn Jewish Hospital for the first time on September 7, 1954, with a chief complaint of intermittent attacks of dizziness of four days' duration. He had been perfectly well until four days prior to admission, at which time, while at work in the early afternoon, he suffered a sudden attack of syncope which lasted for approximately one minute, associated with a "peculiar heartbeat" which the patient could not further describe. He had another similar episode that evening, and the next day had many recurrent similar

bouts, as often as every half hour. He did not lose consciousness during any of these attacks, nor were they accompanied by chest pain, nausea, vomiting, headache or other associated symptomatology.

The patient stated that he had experienced occasional vague pains in the shoulder joints, but otherwise the past history was completely negative. There was no history of fever, recent upper respiratory infection, sore throat or any preceding infection. The history was negative for angina, paroxysmal nocturnal dyspnea, exertional dyspnea, orthopnea or edema. He denied knowledge of previous heart murmurs, rheumatic heart disease, lues, thyroid disease, diabetes or anemia. A review of gastrointestinal, genitourinary, respiratory and neuromuscular status was completely negative.

On admission the patient was a moderately undernourished, well developed young Negro male, alert and coöperative, in no apparent distress and without signs of dyspnea, anemia, clubbing or cyanosis. Temperature was 100.2° F.; blood pressure, 115/60 mm. of Hg; respirations, 20 per minute; radial pulse, 40 per minute, with regular rhythm. The physical examination was completely negative except for the cardiac findings, which were as follows: loud Mi, with M2 partly replaced by a soft diastolic murmur at the apex, with a Grade II apical systolic murmur which was not rransmitted. Jugular pulsations were counted as 80/min. There were no basal murmurs, rubs or thrills.

Cardiac fluoroscopy revealed slight enlargement of the left ventricle but normal pulsation and configuration of the rest of the cardiac contour and great vessels. There was no calcification of any of the valves. Atrial contractions were noted to be 80/min.; ventricular, 40/min. An electrocardiogram taken on admission revealed varying degrees of heart block, from 2:1 to complete. The temperature spiked to 102° F. the day after admission, but reverted to normal the following day and remained so until the patient's death.

Pertinent laboratory findings were: hemoglobin, 11 gm.; white blood cells, 8,800, with 68% polymorphonuclear cells and 32 normal lymphocytes. White blood cells 10 days after admission rose to 14,250 and remained at this level. Sedimentation rate was 33 mm. Mazzini and sickle cell preparations were negative. Blood cultures were sterile, and nose and throat culture revealed Staphylococcus albus, Streptococcus viridans, nonhemolytic streptococcus and diphtheroids. Blood urea nitrogen was 20 mg.%; fasting blood sugar, 99 mg.%; cholesterol, 126 mg.%, with 78% esters; electrolytes were all within normal range. C reactive protein was 4 plus. Urine on admission was normal except for 1 to 2 white blood cells per high power field.

Upon admission of the patient, Duracillin was administered, together with ephedrine sulfate and atropine sulfate, in an attempt to combat the heart block, but the latter drugs produced no sustained effect on the conduction defect. On the assumption that the block might be due to an active rheumatic carditis with inflammatory involvement of the conduction system, a therapeutic trial of cortisone, 75 mg. every four hours, was initiated on the fifth hospital day. Complete heart block persisted for three more days, during which time the patient suffered five episodes of Stokes-Adams seizures, each lasting one to two minutes, with a ventricular rate of 30 to 45/min., associated with unconsciousness and twitching movements of the extremities. However, on the morning of the fourth day of cortisone therapy the complete block was broken and the electrocardiogram showed a varying second degree block with a ventricular rate of 72 per minute and a P-R interval of 0.50 second (0.68 second on previous tracings). Cortisone was then withdrawn and the above pattern persisted for three days, after which a 2:1 block returned and cortisone was reinstituted. The block persisted and two days later, while the patient was still on cortisone, there was reversion to complete block, with evidence of shifting ventricular

pacemakers on the electrocardiogram, and a regular ventricular rate of 28 per minute.

With recurrence of complete block the patient began experiencing frequent attacks of Stokes-Adams seizures, which were treated with ephedrine and atropine. During one of these attacks epinephrine, 1:1000 in intravenous saline infusion, succeeded in producing atrial flutter-fibrillation but had no effect on ventricular contractions.

On the day of death, the patient had four Stokes-Adams attacks with complete asystole lasting 30 to 50 seconds. Treated with atropine, ephedrine and epinephrine,

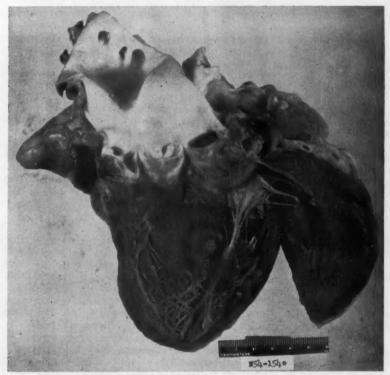


Fig. 1. The aneurysm of noncoronary sinus of Valsalva with thrombus in it. The arrow indicates the pars membranaceus of the interventricular septum covered by blood clots. Note that there are no anomalies other than the variation in the sizes and shapes of the coronary cusps.

the rate stabilized at 50/min., with Cheyne-Stokes respirations. Later that evening the patient went into complete cardiac arrest, which responded briefly to chest percussion and intracardiac needle puncture. Shortly thereafter ventricular fibrillation ensued and did not respond to intravenous Pronestyl, and the patient died on the seventeenth day after admission.

Morphologic Findings: On postmortem examination the pertinent findings were centered in the heart and kidneys. The heart weighed 330 gm. The pericardium was adherent to the epicardium of the anterior surface of the left ventricle near the apex. The epicardial fat was minimal. The right and left auricles were unremarkable.

The foramen ovale was closed. The right and left ventricles measured, respectively, 0.3 and 1.5 cm. in thickness. The chambers were dilated, especially the left ventricle. The myocardium was for the most part not unusual. The tricuspid valve measured 14 cm. in circumference, the pulmonary 8.0 cm., the mitral 11.5 cm. and the aortic 7.0 cm. The valves were smooth and thin except for the noncoronary aortic cusp.



Fig. 2. L.A. denotes left atrium. The aneurysm was ruptured and intramurally dissecting into the myocardium of the left atrium. Note the atrial sacculation and the thrombotic vegetations just above the base of the anterior cusp of the mitral valve. The mitral orifice was distorted by the encroachment of the sacculation.

The chordae tendineae of the atrioventricular valves were delicate and smooth, and the papillary muscles did not appear unusual. The endocardium at the base of the left ventricle just below the aneurysm and the membranous portion of the interventricular septum appeared to be thickened.

The noncoronary aortic sinus was globular in shape, measured 3.5 cm, in its greatest diameter, and distorted the aortic orifice (figure 1). The aneurysm had an

aortic opening about 1.2 cm. in diameter and was completely filled with a brownish and dark red thrombus. Flecks of similar blood clot were seen on the ventricular surface of the saccular cusp and on the membranous portion of the interventricular septum. The saccular cusp, in addition, was thickened and fibrotic. The commissure between this cusp and the left coronary aortic cusp was also thickened; the latter appeared to be compressed by the former, with a consequent distortion of its shape.



Fig. 3. R.A. denotes right atrium. The ruptured aneurysm of the noncoronary sinus of Valsalva was also intramurally dissecting into the myocardium of the right atrium. The sacculation, although it is not prominent in the picture, actually has the same diameter as that of the left atrium. Note the atrial myocardium hemorrhagic area covered by several thrombotic vegetations near the base of the tricuspid valve.

The orifices of the coronary arteries appeared to be unremarkable, and the lumina were patent. The inner lining was smooth. The aorta was studded with minute atheromatous flecks but otherwise presented no features of note.

On dissection, the aneurysm of the noncoronary sinus was ruptured and intramurally dissecting into both atrial myocardia. The intramural thrombus measured 4 cm. in diameter and partly filled the aneurysmal sac described previously. The sacculation of the left atrium, 3.5 cm. in diameter, encroached upon the anterior

cusp of the mitral valve, thereby distorting the mitral orifice (figure 2). The sacculation of the right atrium, of the same size as the left, encroached upon the base of the medial cusp of the tricuspid valve, thereby compressing the corresponding area of A-V node and bundle of His (figure 3). Several thrombotic vegetations, dull gray in color and measuring up to 0.5 cm. in diameter, were seen on the overlying atrial myocardium near the bases of the cusps of the valves described above.

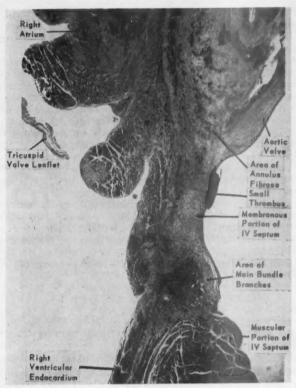


Fig. 4. Photomicrograph under low magnification showing the interventricular septum—compare with figures 1 and 3. In the right upper corner is the area of tangential section of the noncoronary cusp, bordered by the cusp itself on the right, and the right atrium on the left and the annulus fibrosa below. The annulus fibrosa is therefore not well demarcated. Note the hemorrhages in these areas and in the bundle of His, and the blood clot on the membranous portion of the interventricular septum.

No anomalies other than the variations in shapes and sizes of the cusps of the aortic valve were noted.

In the microscopic preparations from the interventricular septum, the area corresponding to the bundle of His was seen to be hemorrhagic, necrotic and infiltrated with a moderate number of pyknotic and karyolytic polymorphonuclear cells (figure 4). The walls of the engorged blood vessels therein were necrotic and, in places, disrupted. These inflammatory cells were seen infiltrating into the crest of the muscular portion of the interventricular septum where the myocardial fibers

and the interstitial fibrocollagenous fibers were markedly swollen. The deeper portion of the septum was also infiltrated with a few large mononuclear cells. The annulus in this area was necrotic and replaced by granulation tissue containing a few polymorphonuclear leukocytes and round cells. The ventricular surface of the membranous portion of the interventricular septum was covered with a clump of fibrin. Above these areas there was a large focus of recent hemorrhage extending into the myocardium of the right atrium and onto the endocardial surface. The myocardial fibers were compressed and necrotic, and the interstitial tissue was markedly edematous and heavily infiltrated with polymorphonuclear cells. The capillaries in this area were markedly engorged. The thrombotic vegetations as seen in the gross specimen contained no bacteria.

In other preparations, the noncoronary cusp was seen to be markedly thickened and composed of hyalinized fibrous tissue and remnants of disrupted elastic fibrils. At one point the fibrin covering the aortic surface of the cusp extended onto the ventricular surface. No bacteria or calcification was noted. There was no evidence of an active inflammation on the commissure or the base of the aorta, nor was there medial necrosis of the latter. The coronary arteries were not unusual.

In both kidneys there were multiple, irregularly wedge-shaped, cortical parenchymal areas which were dull gray-yellow and surrounded by a thin, dark red zone. Microscopically, these areas consisted of ghost structures of tubules and glomeruli and, at the periphery, a dense infiltrate of karyorrhectic polymorphonuclear cells and many engorged blood vessels. The interlobular arterioles thereabout contained fibrin thrombi.

In the rest of the organs there were changes consistent with cardiac failure.

Anatomic Diagnoses: (1) Aneurysm of the noncoronary sinus of Valsalva with
(a) rupture and intramural dissection into the interventricular septum and beneath
the right and left atria and (b) intramural thrombus in the noncoronary sinus, impinging on the tricuspid and mitral valves and with hemorrhage into the conduction
system; (2) multiple infarcts of kidneys; (3) dilatation of heart; (4) congestion of
viscera; (5) edema of the brain.

DISCUSSION

In the absence of any specific evidence of syphilis, subacute bacterial endocarditis, arteriosclerosis or cystic medial necrosis, the aneurysm in this case is considered to be congenital in origin.

The heart block is believed due to infiltration of blood and inflammatory cells into the main conducting fibers. We believe that figure 4 graphically illustrates this point. The response to cortisone, if one can be assumed is attributed to its anti-inflammatory effect upon this portion of the myocardium. This is the first case report in which this entity was treated with cortisone.

Microscopic evidence of rupure and intramural dissection into the left and right atria was found. Clinically, no evidence of rupture of the aneurysm occurred. It is believed that, had the patient lived longer, the aneurysm would have gone on to frank rupture and cardio-aortic fistula formation.

SUMMARY

A case is presented of congenital aneurysm of the posterior or noncoronary sinus (of Valsalva). The clinical picture presented was one of suddenly appearing fluctuating heart block in a young Negro male. On the supposition that inflammation played a role in the heart block, treatment with cortisone was insti-

tuted, which was followed by temporary dissolution of the block. The patient soon went on to complete heart block, however, and died in a paroxysm of ventricular fibrillation.

Autopsy revealed the congenital aneurysm with microscopic infiltration of blood and inflammatory cells into the membranous portion of the interventricular septum.

A brief summary of the literature regarding this rare entity is presented.

SUMMARIO IN INTERLINGUA

Un 32-enne masculo negre esseva hospitalisate a causa del subite declaration de frequente episodios de debilitate, palpitationes, e vertigine quatro dies previemente. Le examine physic revelava un temperatura de 100,2 F, un pulso radial de 40/min, e un pression sanguinee de 115/60 mm de Hg. Le prime sono del valvula mitral esseva accentuate, e dulce murmures systolic e diastolic esseva audibile al apice. Pulsationes jugular amontava a 80/min. Le electrocardiogramma monstrava bloco cardiac variabile del secunde o tertie grado. Roentgenogrammas thoracic revelava leve allargamento sinistro-ventricular. Le numerationes sanguinee esseva normal in essentia.

Quando le therapia a Duracillina, sulfato de ephedrina, e sulfato de atropina non produceva un alteration del defecto de conduction, un curso de cortisona esseva tentate, con le supposition que le bloco cardiac—nunc complete—esseva le effecto de un implication inflammatori del systema de conduction. Le quarte die del therapia a cortisona, le complete bloco se rumpeva in un bloco cardiac del prime grado, con un regular rapiditate ventricular de 72/min. Le administration de cortisona esseva cessate, e le situation persisteva sin cambiamento durante tres dies. Postea un bloco de 2:1 retornava, con frequente accessos de Stokes-Adams. Le patiente moriva in fibrillation ventricular le dece-septime die de su hospitalisation.

Le autopsia revelava un grande aneurysma del noncoronari sinus de Valsalva con dissection intramural a in le septo interventricular in le region del nodo A-V e del major brancas de fasces. Esseva demonstrate un infiltration microscopic de sanguine rubie e de cellulas inflammatori in le area del portion membranose del septo interventricular.

Bloco cardiac con accessos de Stokes-Adams es un rar causa de morte in aneurysma del sinus de Valsalva. Nos opina que le patiente, si ille habeva supervivite plus longe, haberea progredite verso le formation de un fistula cardio-aortic con massive derivation sinistro-dextere.

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BACTERIAL ENDOCARDITIS FOLLOWING MITRAL VALVOTOMY*

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We are reporting a case of bacterial endocarditis which followed cardiac catheterization and mitral commissurotomy. The infecting organism was a hemolytic *Staphylococcus albus* highly resistant to penicillin. The patient recovered with erythromycin and streptomycin therapy.

CASE REPORT

The patient was a 50 year old white male who was first seen on November 27, 1953, because of progressively severe dyspnea. He had had rheumatic fever with polyarthritis at age 16. A heart murmur was heard the following year. He remained well thereafter until 1948, when he fainted after heavy exertion. Subsequently he developed easy fatigue, and dyspnea on exertion. Again a heart murmur was heard, and digitalis was begun. In subsequent years he was able to continue his activities as a salesman, but found that when he omitted the digitalis he became short of breath on walking. In the last two years he had taken digitalis regularly.

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In the last year he had become more and more short of breath, and had developed orthopnea and some loss of appetite. In the last eight weeks there had been dyspnea even at rest. There had never been hemoptysis.

Physical examination revealed a middle aged white male with moderate respiratory distress. Blood pressure was 100 mm. Hg systolic and 60 diastolic. There was no distention of the neck veins. There were moist râles and a few rhonchi in both lower lung fields. The heart was enlarged slightly to the left, with a marked precordial thrust. The rhythm was irregular, with an apical rate of 123 per minute. There was a short, low pitched presystolic murmur at the apex of the heart which was not very loud and which was, indeed, almost impossible to hear at certain times, even after exercise. The liver was enlarged to 5 cm. below the rib margin and was a little tender. The rest of the examination was negative.

The electrocardiogram was abnormal, showing auricular fibrillation. The QRS

axis was shifted to the right.

Fluoroscopy and roentgen films showed moderate, generalized enlargement of the heart, with left atrial and right ventricular enlargement predominating. The mitral valve was heavily calcified. There was moderate pulmonary congestion.

The blood hemoglobin was 15.6 gm. per 100 c.c. The erythrocyte sedimentation rate was 5 mm. per hour (Westergren). The white blood cell counts, differential blood counts and urinalysis were normal. The blood urea nitrogen was 18 mg. per 100 c.c.

On November 28, 1953, the patient was admitted to the hospital, where the administration of mercurial diuretics, together with digitoxin, bed-rest and a 400 g, sodium diet, resulted in the loss of 11 pounds of fluid, the disappearance of the râles and liver enlargement, and slowing of the ventricular rate to 74 per minute. When the rate slowed it was possible to hear a low, rumbling, soft, early and mid-diastolic murmur at the apex, and also a soft systolic murmur at the apex.

Cardiac catheterization was carried out on December 3, 1953. Introduction of the catheter through the left arm met with obstruction in the axilla, and the No. 8 F. catheter was therefore introduced via a right antecubital vein. During manipulation of the tip in the right atrium the outer coat of the catheter cracked at the junction with the adapter attached to the strain gauge. This catheter was therefore removed and another substituted. The remainder of the procedure was without incident. Pressure records using the Statham strain gauge revealed moderately elevated pressures, those in right ventricle averaging 40 mm. Hg systolic and 1 mm. Hg diastolic. The pressure in the right atrium averaged zero. Procaine penicillin was administered following the catheterization, 300,000 units every 12 hours intramuscularly for four days.

On December 10 mitral commissurotomy was performed by Dr. Jensen. Procaine penicillin, 300,000 units intramuscularly every 12 hours, was started preoperatively and continued for 14 days. The left pleural cavity was found to be obliterated by adhesions. The pulmonary artery was enormously enlarged and very taut. The pulmonary veins were also enlarged. There was a diastolic thrill over the left ventricle. Thrombi were found in the auricular appendage and removed. The mitral valve was found to be very heavily calcified and thickened, with the orifice just admitting the tip of the finger. A mild regurgitant stream was felt. The lateral commissure, which was fused for a distance of about 3 cm., was gradually opened by finger fracture. Nodular areas of calcification were felt all along the commissure. As the commissure was gradually opened the finger palpated granular material, probably calcium, crumbling along the fracture line. The lateral commissure was opened by finger fracture all the way to the valve ring, creating an opening extending two and one-half fingerbreadths. The regurgitant stream was then less marked than before the opening of the commissure. The surgeon's glove was torn over the operating

finger during the actual opening of the commissure. The carotid arteries were compressed during the manipulations on the auricular appendage and the valve.

The patient's course after surgery was rather stormy for the first 24 hours, with a very rapid ventricular rate (150 per minute), a blood pressure of 90 mm. Hg systolic, and 64 diastolic, mild cyanosis and cool extremities. Considerable bloody drainage continued from the chest catheters, requiring further blood transfusions. After 12 hours the blood pressure had risen to 120 mm. of Hg systolic and 85 diastolic, and by the next day his condition had improved considerably.

The course over the first eight postoperative days was complicated by recurring mental confusion, delusions and disorientation. During this time a moderate hypochloremia (as low as 81 mEq./L.) and a less marked hyponatremia (as low as 129 mEq./L.) occurred. Following recovery from this his course was uncomplicated. He was discharged from the hospital on December 26, at which time he had been afebrile for four days. At home he continued to take penicillin orally, 200,000 units twice a day, as a prophylaxis against hemolytic streptococci.

Sections of the auricular appendage showed organizing thrombi and thickening of the endocardium. The epicardium was thickened in places, and infiltrated with mononuclear cells. The myocardium was normal. There were no Aschoff's bodies.

 ${\rm TABLE} \ 1^{*}$ Sensitivity of the Staphylococcus Isolated from the Blood in This Case

Antibiotic	Sensitivity
Neomycin	0.195 microgram per c.c.
Oxytetracycline	0.39 microgram per c.c.
Chlortetracycline	0.39 microgram per c.c.
Erythromycin	0.78 microgram per c.c.
Carbomycin	1.56 microgram per c.c.
Bacitracin	3.12 micrograms per c.c.
Streptomycin	3.12 micrograms per c.c.
Chloramphenicol	6.25 micrograms per c.c.
Penicillin	500 units per c.c.

^{*} Courtesy Dr. Robert Wise.

The patient remained well at home until January 8, 1954, 29 days after the commissurotomy, when he developed anorexia, mild chills and low grade fever. There were no petechiae, and the spleen was not palpable. The chills recurred at 24 to 48 hour intervals, with temperature rising to 101° F. On January 14 the spleen was definitely palpable. The patient was re-admitted to the hospital with the presumptive diagnosis of bacterial endocarditis.

Following his re-admission to the hospital he became weaker each day, with fever ranging to 102.4° F., increasing enlargement of liver and spleen, rise in heart rate, and appearance of mild edema of the feet. The apical diastolic murmur remained unchanged. The apical systolic murmur increased somewhat in intensity.

Of nine blood cultures taken in the first four days, five showed growth of Staphylococcus albus. All of these organisms were hemolytic, but coagulase was negative. On plate-disc sensitivity studies this staphylococcus was said to show the greatest sensitivity to neomycin, streptomycin and erythromycin, and lesser sensitivity to oxytetracycline, chlortetracycline, chloramphenicol and bacitracin, and least sensitivity to penicillin, although a definite clear band of perhaps 5 mm. surrounded the penicillin disc. The organism was resistant to polymyxin-B. Tube culture sensitivity studies proved that the organism was highly resistant to penicillin, with growth occurring in the presence of 50 units per cubic centimeter. The tube culture sensitivities are shown in table 1.

On January 19 the patient was started on this regimen: (1) erythromycin, 0.5

gm. every six hours orally; (2) erythromycin, 0.5 gm. in 500 c.c. of 5% glucose slowly intravenously every 12 hours; (3) streptomycin, 0.5 gm. intramuscularly every 12 hours. Improvement was prompt, striking and continuing. The temperature, which previously had reached 101 to 102° F. daily, declined to normal in 48 hours, where it remained throughout the four week course of treatment, except for a spike to 100.8° F. on the sixth day of treatment. The patient became steadily stronger as the râles, liver enlargement and edema disappeared; his appetite improved, and the ventricular rate fell to 72 per minute. Petechiae never appeared. The antibiotic regimen was continued for four full weeks. At the time of his discharge on February 17 the spleen had decreased in size but was still palpable 1.5 cm. below the rib margin; the systolic apical murmur was softer, but the diastolic murmur remained the same. The patient was ambulatory when discharged.

His strength thereafter gradually improved, so that he was able to begin halftime work in March 1954, and full time work in April. In September he was able to paint his basement. Several bouts of gall-bladder colic occurred during the summer of 1954, and finally it became necessary to perform a cholecystectomy in October. At the time of writing, one year after treatment of the endocarditis, the patient is alive and well.

Case Summary: This is the case of a 50 year old male who developed bacterial endocarditis following cardiac catheterization and mitral commissurotomy. The organism was a S. albus, hemolytic, coagulase negative, highly resistant to penicillin. Recovery followed therapy with erythromycin orally and intravenously, and streptomycin intramuscularly.

COMMENT

There have been remarkably few reported cases of bacterial endocarditis after mitral commissurotomy in proportion to the widespread performance of this operation. Bailey et al. in 1952 reported the occurrence of bacterial endocarditis in two patients after mitral valve surgery in a series of 706 cases. Stapleton et al. reported two cases of presumed endocarditis, one following mitral commissurotomy, the other after pulmonic valvotomy. No positive blood cultures were obtained in these two cases. Both recovered after antibiotics. Brunsdon et al. reported one case of fatal endocarditis due to *Pseudomonas pyocyanea* after mitral valvotomy, from a series of 150 cases. Andrus et al. reported one death from staphylococcic pericarditis in a series of 75 mitral valvotomies. Panting et al. reported one case of bacterial endocarditis after mitral valvotomy due to *S. aureus*.

In our case it is theoretically possible that the infecting organism may have been introduced during the cardiac catheterization. Winchell ⁶ reported a case of bacterial endocarditis following, and probably due to, cardiac catheterization. However, there was in the present case no recognized break in sterile technic during the catheterization, whereas there was an obvious and direct exposure of the valve to the surgeon's exposed finger when his glove was torn on the calcified valve. The ubiquity of the staphylococcus and the difficulty in producing complete sterility of human skin by surgical scrub are well known. The weight of evidence here points to the implantation of the infecting organism at the time of commissurotomy.

Even without an obvious break in the surgeon's gloves there is danger of contamination of the wound during valvotomy because of the possibility of un-

detected tiny breaks in the rubber gloves. Devenesh and Miles,⁷ for instance, reported in a series of wound infections due to staphylococci that the infections probably occurred as a result of tiny undetected punctures of the rubber gloves of one of two surgeons using the operating theater who harbored virulent staphylococci in his skin. They found that minute puncture of the gloves occurred

in as high as 14%, even after careful precautions were taken.

The growing problem of antibiotic-resistant staphylococal infections has been widely reviewed and documented.8-11 Resistance to the individual antibiotics has appeared in proportion to the use of the antibiotic in the community.¹² The steady increase in the percentage of staphylococci resistant to penicillin has made this organism the most troublesome problem in the therapy of bacterial endocarditis. It is noteworthy that in our case infection of the endocardium by a penicillin-resistant staphylococcus occurred during a period when penicillin was being administered continuously. The mortality from staphylococcic endocarditis was relatively high even early in the antibiotic era; about 50% mortality in the period from 1943 to 1952,13 when penicillin and streptomycin (and, latterly, chlortetracycline) were available. With the increasing percentage of staphylococci resistant to penicillin the mortality rate became even higher. Spink,8 for instance, reported that by the period 1952 to 1953 the mortality in staphylococcic endocarditis in his cases reached 90%. Use of the bacteriostatic agents chlortetracycline, oxytetracycline and chloramphenicol has produced cure in additional cases where penicillin was ineffective, but has been disappointing in many cases.14 Other antibiotics have proved effective in isolated cases. For instance, Reed and Wellman 15 have reported a cure with neomycin when the infecting staphylococcus was resistant to penicillin, streptomycin, oxytetracycline, chlortetracycline, polymyxin and chloramphenicol. Friedberg and Bader 16 reported a cure after addition of bacitracin to a regimen of penicillin, chlortetracycline and chloramphenicol.

The optimism over the potent effect of erythromycin in staphylococcic infections has been tempered by the failure of the drug in most cases of staphylococcic endocarditis (particularly if used alone), and the rapid appearance of resistant organisms.^{14, 17–19} Geraci and Martin ²⁰ reported the death of four out of four cases of staphylococcic endocarditis treated with erythromycin. Other

antibiotics also were tried in these cases.

Erythromycin may work synergistically with the actively bactericidal agents, bacitracin and streptomycin. 21, 22 Such combined erythromycin and streptomycin therapy has been reported to have failed in two cases of staphylococcic endocarditis, but intravenous therapy was not used. 17 Combined therapy with erythromycin, oxytetracycline intravenously and orally, and streptomycin parenterally was reported to produce a cure in one case after penicillin combined with streptomycin had failed. 28 In our case erythromycin was given intravenously as well as orally in an attempt to produce very high blood levels, 24 in view of the difficulty in producing bactericidal levels of this antibiotic by the oral route. 25, 26 Streptomycin was combined with the erythromycin in an attempt to prevent the development of resistance 27 and for its possibly synergistic effect. The prompt response to therapy and continued good health of the patient leave no doubt that this combination was curative.

It may be that the high blood levels of erythromycin obtainable by intravenous

administration will produce better results than have been obtained with oral therapy in the past. In view of the poor results with erythromycin alone in bacterial endocarditis, and the rapid emergence of resistant organisms, particularly staphylococci, it should not be used unless the organisms are highly resistant to penicillin and highly sensitive to erythromycin, and should then be used only in combination with other antibiotics, notably streptomycin and bacitracin. Further trials are needed to decide whether such combined erythromycin therapy is as effective as the broad spectrum antibiotics, the tetracyclines and chloramphenicol, in penicillin-resistant staphylococcic endocarditis.

The fact that bacterial endocarditis can occur after valve surgery should emphasize the importance of antibiotic therapy during such surgery, and also the importance of vigorous combined antibiotic therapy whenever there is an unavoidable break in sterile technic during surgery. The cut or fractured valve is probably more susceptible to bacterial infection.¹ The low incidence of endocarditis after valvotomy probably reflects careful modern surgical technic, and the common use of antibiotics during surgery and the postoperative period.

The physician should be alert to the possibility of bacterial endocarditis following valvotomy, so that early detection may improve the chances for recovery.

SUMMARIO IN INTERLINGUA

Isto es un reporto de un caso de endocarditis bacterial post catheterisation cardiac e commissurotomia mitral. Le prime symptomas del endocarditis appareva 29 dies post le commissurotomia. Le organismo infective, recovrate ab cinque separate culturas sanguinee, esseva un Staphylococcus albus, que esseva hemolytic, negative in coagulase, e extrememente resistente a penicillina. Illo esseva multo sensibile a neomycina, oxytetracyclina, chlortetracyclina, e erythromycina; illo esseva minus sensibile a carbomycina, bacitracina, e streptomycina. Un regime de erythromycina intravenose e oral e de streptomycina intramuscular de quatro septimanas de duration produceva un prompte responsa e un sanation confirmate per le facto que le patiente esseva in bon stato de sanitate un anno post le tractamento.

Le datos obtenite in iste caso pare indicar infection del valvula al tempore del operation. Le uso intravenose de erythromycina esseva possibilemente un importante ration pro le successo del tractamento. Le uso de streptomycina con erythromycina esseva etiam possibilemente un factor importante, o via un synergetic effecto antibacterial o per prevenir le disveloppamento de resistentia a erythromycina. Viste le pauco bon resultatos obtenite per erythromycina in endocarditis bacterial secundo le reportos de altere autores, experientias additional con erythromycina intravenose debe esser colligite ante que su efficacia pote esser considerate como demonstrate.

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SEVERE SYSTEMIC REACTIONS TO PARA-AMINOSALICYLIC ACID: A CASE REPORT AND REVIEW OF THE LITERATURE *

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MILD, untoward reactions to standard doses of para-aminosalicylic acid (PAS) are common. They consist for the most part of symptoms of gastrointestinal irritation. A detailed study by Cannemeyer, Thompson and Lichtenstein 1 has disclosed a less frequent but more severe pattern of hypersensitivity, consisting of fever, chills, pruritus, skin rash, conjunctivitis or pharyngitis, and lymphadenopathy. The incidence of these hypersensitivity reactions is reported to be approximately 2.5%.2 Hepatosplenomegaly 1,8 and Löffler's syndrome 3,4 are rare manifestations. Hypersensitivity reactions generally develop eight to 45 days after onset of therapy with PAS.5 Laboratory evidence of toxic hepatitis, when present, follows the appearance of untoward reactions in from three to seven days.1, 6

Laboratory studies reveal evidence of eosinophilia ranging from 7 to 76%, with the majority of cases studied reported to be around 25%.1 Pertinent data relating to deranged liver function, 1,8 urinary tract dysfunction 5 and adrenal cortical insufficiency thave been mentioned in the literature. Steininger, Klopfenstein and Woodruff 7 report one fatality resulting from PAS sensitivity, attributed to insufficiency of the adrenal cortex.

When PAS sensitivity is suspected, a single provocative dose of 1 to 5 gm. of PAS is generally given with caution, to confirm the diagnosis.1,7 A PAS patch test may be used but is seldom of diagnostic aid.⁵

CASE REPORT

This 42 year old Negro male was admitted to the Veterans Administration Hospital, Madison, Wisconsin, on December 29, 1954, with the tentative diagnosis of pulmonary tuberculosis. Two months prior to admission he had developed a cough productive of four ounces of yellow sputum daily. One month prior to admission he had a chest x-ray at another hospital and was referred here as a tuberculosis suspect.

Past History: The patient had consumed large amounts of alcohol for several years, admitting to one quart of wine daily. He had been hospitalized on two occasions in the last eight months because of chronic alcoholism and delirium tremens. A liver biopsy performed on May 11, 1954, revealed "marked fatty metamorphosis with metamorphosis being the prominent picture. Diagnosis: Early fatty cirrhosis

Physical Examination: The patient was a fairly well developed, fairly well nourished Negro male. Gross tremors of the hands were evident. On chest examination there were numerous moderately coarse râles over the apical and posterior segments of the right upper lobe, especially prominent after coughing. The remainder of the physical examination was not contributory.

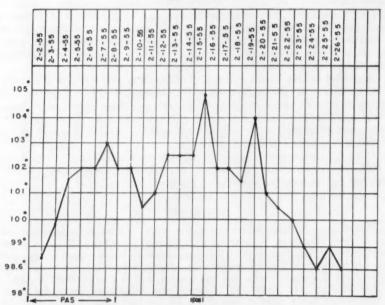
^{*} Received for publication July 11, 1955. From the Veterans Administration Hospital, Madison, Wisconsin.

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A chest roentgenogram taken on December 29, 1954, revealed pulmonary inflammatory disease, chiefly on the right, which was relatively poorly defined and therefore believed to be active. Sputum smears and cultures taken on admission were positive for tubercle bacilli.

Hospital Course: On January 6, 1955, the patient was started on INH, 100 mg. three times a day, and PAS, 4 gm. three times a day. His course was uneventful until February 4, 1955, when he complained of generalized myalgia, with the greatest severity in the left flank. His temperature at this time was 101.5° F. The febrile course continued (table 1), and on February 7, 1955, a pruritic maculopapular rash appeared on his arms and hands. On February 8, 1955, he showed evidence of acute

TABLE 1
Temperature Course



pharyngitis, and the PAS was discontinued. A white cell count with differential revealed a slight leukopenia (5,450), with an absolute eosinophilia (16%). Albumin, white blood cells and red blood cells were present in the urine. Although the febrile course continued, the patient had no specific complaints until February 15, 1955, when 8 gm. of PAS were inadvertently given (in divided dosage). He complained of sudden right upper quadrant pain, generalized myalgia and nausea. The liver, spleen and axillary lymph nodes were palpable. His sclerae appeared icteric and his temperature spiked to 104.8° F. The blood picture 48 hours after the 8 gm. dose revealed a leukocytosis, neutrophilic left shift and eosinophilia (27%). Liver function studies were abnormal (table 2). A chest roentgenogram demonstrated that the pulmonary inflammatory lesions had cleared since the examination of December 29, 1954. Left axillary node and liver biopsies were performed on February 18 and February 23, 1955, respectively. Reports were as follows:

Lymph Node (figure 2): "The lymph node is loosely organized and there is some disturbance of architecture. There appears to be a marked proliferation of reticular elements as well as some increase in fibrous tissue. An occasional germinal center may be distinguished; these are rather small. Polymorphonuclear leukocytes are identified, fairly frequently, sometimes in small numbers, and sometimes focally grouped; these form a distinct feature. Eosinophilic polymorphonuclear leukocytes are not present in numbers larger than might be expected from the distribution of the inflammatory infiltrate. There are several cells with hypochromatic nuclei. Diagnosis: Subacute lymphadenitis with reticular hyperplasia."

Liver (figure 3): "The lobular architecture is considerably obscured by proliferation of new connective tissue, primarily about portal spaces. There is, in addition, active infiltration of tissue with polymorphs, lymphocytes, and plasma cells. Fatty changes in this specimen are minimal. Diagnosis: Active hepatitis with early cirrhosis."

TABLE 2

				Lal	poratory D	ata						
Date	1954	1955										
	12-31	2-9	2-16	2-17	2-21	2-22	3-1	3-4	3-9	3-18	3-24	4-5
Cephalin floc. Thymol turbidity units	1		++++		++++		++++		+++		+++	++
Alkaline phosphatase K.A. units			20		23		15		10.8		13.5	
Total serum proteins gm.%	6.9				7.3		8.1		8.1		7.7	
A/G ratio Prothrombin time % of normal	1.3 86				0.7 41	72	0.8		1.0	100	1.2	
Total serum bilirubin	1.5		3.0		6.0		2.1				1.0	
Heterophile antibody titer (pos. in dilu- tion)			_	1:14	1:7							
WBC (thousands) Eosinophilia % Hematocrit	12.8 1 45	5.4 16 43	13.7	16.3 27 38	11.0 21 40			10.5 14 45		6,5 9 46		

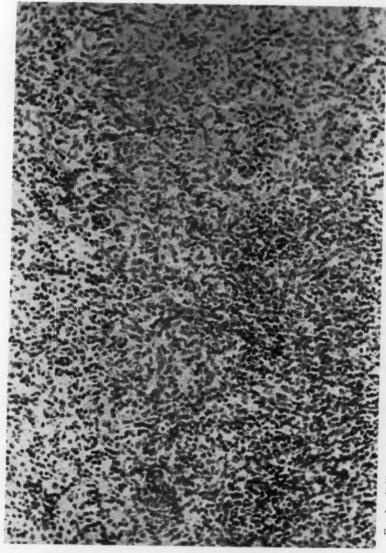
By March 1, 1955, the liver had definitely decreased in size, and the spleen and lymph nodes were no longer palpable. The blood picture and blood chemistry findings were returning toward normal. A patch test was positive to PAS.

Discussion

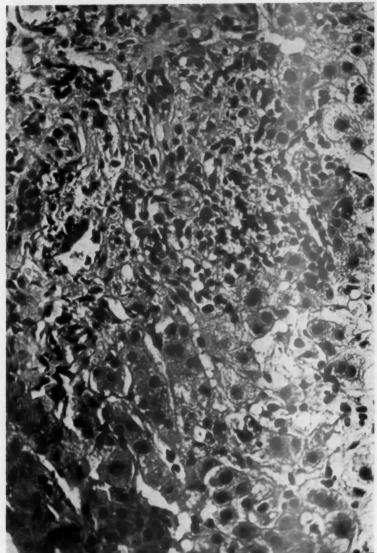
The initial features of this case were compatible with a PAS hypersensitivity reaction. The impression was substantiated by the responses to the 8 gm. dose of PAS which precipitated an acute illness characterized by fever, myalgia, hepatosplenomegaly and lymphadenopathy. The positive patch test further supported the diagnosis.

The initial impressions—acute pyelonephritis and acute pharyngitis—indicate the bizarre character of this syndrome. With the onset of jaundice, viral hepatitis and infectious mononucleosis were added to the differential diagnoses. The appearance of the signs and symptoms approximately one month following the institution of PAS therapy, together with the eosinophilia, leads to the impression of hypersensitivity to PAS.

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Axillary node biopsy, February 18, 1955, showing prominent reticular hyperplasia. The remaining cells are mononuclear, chiefly lymphocytes, with occasional plasma cells. ×220.



Fro. 2. Liver biopsy, February 23, 1955. The portal space to the left shows chiefly a proliferation of the connective tissue cells extending into the adjacent hepatic parenchyma. Occasional plasma cells and lymphocytes can be seen in the connective tissue. \times 440.

The severity of the reaction is indicated by the anatomic changes observed in the biopsies of the lymph node and liver. The changes are similar to those described by Cannemeyer, Thompson and Lichtenstein. The early connective tissue growth is possibly indicative of the initial PAS hypersensitivity reaction. This point is inconclusive, however, since the patient had evidence of liver damage prior to this hospitalization. The recent cellular infiltration is more certainly representative of an acute superimposed effect, caused by the inadvertently given 8 gm. dose of PAS.

It is apparent that the out-patient treatment of pulmonary tuberculosis is increasing, and that PAS remains an established drug in the treatment of this disease. These facts, accompanied by the occasional systemic reaction that occurs with PAS therapy, should alert the physician to the complexity and the severity of this syndrome.

CONCLUSIONS

1. A case of para-aminosalicylic acid hypersensitivity is presented.

2. The clinical picture, hematologic study, abnormal liver function tests, urinalysis derangement and tissue changes are included.

3. Increased out-patient treatment of pulmonary tuberculosis demands increased alertness to the possibility of a severe systemic hypersensitivity reaction to PAS.

SUMMARIO IN INTERLINGUA

Es presentate le historia de un caso de sever reactiones a acido para-amino-salicylic (PAS). Le patiente, un masculo negre de 42 annos de etate, habeva essite sub tractamento con PAS e isoniazido durante circa un mense quando ille disvelop-pava myalgia generalisate, febre, e—alicun dies plus tarde—un pruritic eczema maculopapular e pharyngitis acute. Studios sanguinee revelava leve grados de leuco-penia e eosinophilia (16%). Albumina e rubie e blanc cellulas sanguinee esseva presente in le urina. Le curso de PAS esseva interrumpite. Le patiente deveniva asymptomatic ben que le febre continuava. Un septimana plus tarde, PAS esseva usate de novo. Postea le patiente disveloppava febre "apiculate," myalgia generalisate, nausea, jalnessa, e dolores del quadrante dextero-superior. Esseva trovate que ille habeva lymphadenopathia, hepatomegalia, e splenomegalia. Biopsias de un nodo lymphatic e del hepate revelava provas de acute inflammation. Nulle administration subsequente de PAS esseva interprendite, e le symptomas del patiente se clarificava rapidemente. Le temperatura retornava al norma. Le splen, le hepate, e le nodos lymphatic regredeva a dimensiones normal.

Es includite un revista del litteratura in re reactiones a PAS.

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TUBERCULOUS AXILLARY ADENITIS FOLLOWING APPLICATION OF P.P.D.*

By John J. Walsh, M.D., Richard H. Linn, M.D., New Orleans, Louisiana, and Frank Brancato, Ph.D., Seattle, Washington

MUCH has been written of the clinical application of skin testing with purified protein derivative (P.P.D.) tuberculin, and the ramifications thereof. However, limited examination of the literature fails to reveal the report of a case of axillary tuberculous adenitis subsequent to skin testing with P.P.D. For this reason the following case is reported in its entirety.

CASE REPORT

This 50 year old Negro seaman was admitted to the U. S. Public Health Service Hospital, Seattle, Washington, July 31, 1953, with the chief complaint of "a painful knot in my right armpit" of 24 days' duration. On June 3, 1953, routine chest roentgenogram was interpreted as abnormal and the patient was referred to a clinic for evaluation. Repeat x-rays performed at the latter facility were interpreted as revealing old inflammatory changes in the third right interspace and left parahilar regions. These films were compared with the only previous x-ray, a 70 mm. photofluorogram taken in 1949, and interpreted as essentially unchanged, although there may have been some slight decrease in the left parahilar mass, in the examiner's opinion. Several sputum studies were reported as negative on smear and culture. A P.P.D. skin test was applied to the right forearm, immediately after which the patient stated he was informed that he had been given "the strong test" erroneously. Parenthetically, it may be stated that subsequent investigation revealed that only P.P.D. is used in this clinic and that no similar complications were reported. Moreover, the patient is recorded to have been given a P.P.D. skin test of intermediate strength. Within 12 hours the patient noted aching in the right axilla, followed by slowly enlarging tender masses in this area, resulting in hospitalization on the twentyfourth day. The area of injection exhibited swelling, tenderness and warmth but failed to necrose. The patient denied constitutional symptoms. Past history and system review were negative.

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Examination revealed in the right axilla a 5 by 4 by 3 cm. mass of matted, tender, moderately firm lymph nodes with a small central area of fluctuation. There was an indurated macular area of approximately 2 cm. on the flexor surface of the right arm at the site of the skin test. It appeared to have been of 3 plus intensity and without necrosis. The only other abnormality was clubbing of the fingers, which the patient insisted repeatedly was familial in origin and lifelong in duration.

Serologic test for syphilis and urinalysis were negative. The hemogram was normal with the exception of an erythrocyte sedimentation rate of 42 mm. Ducrey's and Frei's skin tests were negative. Chest roentgenogram revealed prominent markings throughout, especially in the third right interspace and left hilar region. Moreover, irregular calcifications were superimposed on the left lung root, with an ir-

regular density extending downward and outward from the root.

On August 4 and August 7, 1953, under local anesthesia, the fluctuant area was aspirated and a total of 8 c.c. of thick, brownish yellow purulent material was removed. The patient then left the hospital against medical advice prior to completion of studies. Examination of the material for fungi and ordinary bacteria was negative on smear and culture. However, the smear of each specimen contained several acid-fast bacilli. The first on culture (both on Lowenstein's and Petragnani's media) revealed typical acid-fast bacilli which were later demonstrated to be pathogenic for guinea pig. The second specimen produced typical acid-fast bacilli on Petragnani's but not on Lowenstein's media when cultured. The positive culture obtained only with Petragnani's media was subsequently demonstrated to be pathogenic for guinea pig. One gastric wash failed to reveal acid-fast bacilli on culture.

Later it was learned that after leaving the hospital the patient was treated symptomatically in conjunction with antibiotics in the form of penicillin and sulfonamides, with gradual subsidence of signs and symptoms. Because of the previously mentioned bacteriologic findings, the patient was hospitalized in another hospital for evaluation. Complete studies, including gastric washings and bronchoscopy, were negative, and

the patient was discharged fit for duty.

On February 18, 1954, the patient was re-admitted to the U. S. Public Health Service Hospital, Seattle, complaining of weakness of the back, easy fatigability, lassitude and exertional dyspnea. He denied other symptoms. Examination revealed the previously noted clubbing of the extremities, transitory rhonchi in both lung fields, and thickening of the subcutaneous tissues of the right mid-axilla overlying several small, firm, nontender, semi-fixed nodes. The patient gave a 3 plus reaction to histoplasmin but no reaction to coccidioidin. Hemogram was normal except for an erythrocyte sedimentation rate of 25 mm. per hour. Circulation time and venous pressure were normal. Vital capacity was approximately 60% of normal. Chest roentgenograms were essentially unchanged when compared with those obtained during hospitalization in August, 1953. Intravenous pyelogram was within normal limits, although x-rays of the lumbosacral spine and pelvis revealed complete fusion of the right sacro-iliac joint. Three gastric washings were obtained, as were three 24-hour urine specimens and three sputum specimens for bacteriologic studies. The sputa contained a few minimally atypical cells, probably inflammatory in nature, but failed to reveal tubercle bacilli on smear or culture. All urine cultures were negative. Although two gastric washings failed to reveal growth on culture, the third specimen resulted in the growth of several identical colonies which were slightly yellow and somewhat mucoid. Growth occurred on all three media (Lowenstein, Petragnani and blood agar). Smears of these colonies contained atypical acid-fast organisms. Three guinea pigs, inoculated with material obtained from these colonies, revealed no abnormalities when autopsied after six weeks of observation. Since the neutral red test was positive, a chicken was inoculated but failed to present abnormal findings on postmortem examination. It was concluded the organisms obtained from the gastric

wash were nonpathogenic acid-fast bacilli and of no clinical significance. Again, after a hospital course marked only by lack of coöperation, the patient left the hospital against medical advice prior to bronchoscopy and other planned studies.

DISCUSSION

Two facts stand out on review of this case. Following skin testing with intermediate strength of P.P.D. there developed a purulent axillary adenitis from which on two occasions tubercle bacilli were obtained on smear and culture. Moreover, subsequent guinea pig inoculation demonstrated the pathogenicity of the organisms recovered. It is conceivable that the entire episode represents Koch's phenomenon occurring after accidental inoculation with viable tubercle bacilli. This is most improbable on statistical and clinical grounds. It would appear more logical to postulate that the phenomenon represents an allergic reaction to P.P.D. involving glands previously infected with tubercle bacilli. Constitutional symptoms and transitory exacerbation of pulmonary lesions have occurred on occasion following skin testing. It is thought that the case in question represents a ramification of the allergic state. Although the patient is recorded as having been given the intermediate strength P.P.D., the possibility exists that in fact a much stronger concentration of the substance was used due to incorrect dilution. This is not probable, since the test was done in an established clinic where an experienced nurse prepared and injected the material. Moreover, others tested on the same day were not noted to have experienced unusual difficulties.

SUMMARY

Following skin testing with intermediate strength P.P.D. a patient suffering from minimal inactive pulmonary tuberculosis developed regional axillary adenitis from which virulent tubercle bacilli were removed on two occasions.

SUMMARIO IN INTERLINGUA

Suppurative adenitis axillari regional se disveloppava in un patiente brevemente post le application de un test cutanee de tuberculina a purificate derivato de proteina. Studios bacteriologic del aspirato, incluse inoculation cultural e animal, resultava in le isolation de typic bacillos tuberculotic que esseva pathogenic in porcos de India e habeva omne le characteristicas de Mycobacterium tuberculosis var. hominis. Extense studios clinic e laboratorial non succedeva a demonstrar le presentia de tuberculosis active in altere partes del corpore del patiente. Ille se restabliva con solmente supportative mesuras therapeutic.

Nos opina que iste caso representa le activation de glandulas previemente inficite e continente bacillos tuberculotic al tempore del test. Le mechanismo esseva probabilissimemente un mechanismo de hypersensibilitate. Le examine del litteratura non revelava un caso comparabile.

EDITORIAL

ADRENAL CORTICAL FUNCTION AND THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

For a long time clinical investigators have postulated that the etiology of rheumatoid arthritis might have metabolic implications. At one time the parathyroid glands were considered to have an important relationship to the disease, and it was believed that parathyroid dysfunction caused the changes in the bones and joints. Hyperthyroidism and hypothyroidism have likewise been considered to have an etiologic linkage in the pathogenesis of this disease. Careful studies, however, have failed to reveal a relationship of any of these endocrinologic disorders to rheumatoid arthritis.

On the other hand, there are certain clinical characteristics of the disease, i.e., profound muscle weakness, lassitude, frequent attacks of hypoglycemia, and occasional spectacular skin pigmentation, that have led to the implication of adrenal cortical dysfunction in its etiology. These observations, together with the report of profound clinical improvement that readily results from the administration of corticotropin and the 11, 17 oxygenated corticoids, have brought this problem into sharp focus. Since Hench's electrifying report in 1949 on the clinical effect of cortisone in rheumatoid arthritis, investigators have attempted to assess the part played by the adrenal-pituitary interrelationship in this disease state.¹

There are several characteristics of the clinical response to such therapy that led early investigators to postulate that this was a deficiency disease that could be rectified by the administration of the 11, 17 oxygenated adrenal steroids. The clinical improvement, usually apparent within a matter of hours, cannot all be attributed to the known anti-inflammatory effect of the drug. In fact, several days may elapse before discernible histological evidence of change appears in the joint structures. Soon after administration of an oral or parenteral dose of cortisone the patient begins to lose the chronic fatigue and lassitude clinically characteristic of this disease state. The patient again appears mentally alert, although he may have been depressed previously. The joint pain and muscle stiffness, both hallmarks of the disease, abate before any objective evidence of improvement in the diseased joints occurs. Likewise, even though the joint manifestations of the disease never completely resolve, the patient may be able to resume normal or almost normal activity.

Similarly, there is a marked exacerbation of the disease soon after sud-

¹ Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effect of hormone of adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenal corticotropic hormone on rheumatoid arthritis; preliminary report, Proc. Staff Meet., Mayo Clinic 24: 181–187 (April 13) 1949.

den termination of therapy with cortisone or related drugs. The severity of the exacerbation frequently far exceeds the original activity of the disease. Systemic reactions, such as fever, are usual and the joint involvement may increase and spread to involve those previously apparently free of the disease. This exacerbation occurs during the maximum suppression of activity of the adrenal cortex that results from the administration of the exogenous steroid. A similar situation is often seen after surgical operations, burns, or other trauma occurring in patients with rheumatoid arthritis. Here, again, for several days immediately after the stressing episode, the disease may appear improved only to relapse later with augmented fury.

On the other hand, if adrenal cortical insufficiency is implicated in the pathogenesis of the disease, it would appear that arthritis would be a common finding in patients with Addison's disease. Such is not the case; in fact, joint disease is in reality a rarity in this disease syndrome.2 Further, no characteristic morphologic changes have been found in the adrenal cortex

in rheumatoid arthritis.8

Several attempts have been made to evaluate adrenal cortical function in patients suffering with this disease. Unfortunately the results of these studies have not been very enlightening. The indices of adrenocortical function, as demonstrated by the amount of metabolites of the adrenal steroids in the urine, have been studied in patients with rheumatoid arthritis. One study found the urinary 17-ketosteroid excretion to be normal in 11 patients with peripheral rheumatoid arthritis, but to be elevated above the anticipated normal values in 35 patients with rheumatoid spondylitis.4 However, other workers failed to find elevated values in eight patients with rheumatoid spondylitis, and found values in the normal range in 76% of 67 patients with peripheral rheumatoid arthritis.5 Hench and co-workers found values below the normal range in only 29% of their patients with the disease syndrome.6 Still other workers have reported mean values in groups of patients with rheumatoid arthritis to be about one-half of those obtained in a control group of normal subjects.7

Determinations of urinary corticoid excretion have been equally uninformative. Howard et al. found subnormal levels by bio-assay in all of

² Perera, G. A., and Ragan, C.: Hypoadrenalism: Steroidal mediation of sodium action

² Perera, G. A., and Ragan, C.: Hypoadrenalism: Steroidal mediation of sodium action on blood pressure; modification of antiarthritic response to cortisone, Proc. Soc. Exper. Biol. and Med, 75: 99-103 (October) 1950.
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 ⁴ Davison, R. A., Koets, P., and Kuzell, W. C.: Excretion of 17-ketosteroids in ankylosing spondylarthritis and in rheumatoid arthritis; preliminary report, J. Clin. Endocrinol. 7: 201 (Mar.) 1947.
 ⁵ Desmarais, M. H. L.: The neutral 17-ketosteroids in rheumatoid arthritis and spondylitis, Ann. Rheumat. Dis. 8: 296 (Dec.) 1949.
 ⁶ Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions; a study in clinical physiology, Arch. Int. Med. 85: 545 (Apr.) 1950.
 ⁷ Freund, H. A., Bazinski, D. H., and Scott, R. B.: 17-ketosteroid excretion in rheumatoid arthritis, J. Michigan M. Soc. 49: 1076 (Sept.) 1950.

nine patients with rheumatoid arthritis; in six of these, urinary corticoids were also determined by a chemical method and found to be decreased.8 In contrast, values in the normal range were found in an unspecified number of patients with rheumatoid arthritis.6,9

It is readily apparent that the results of such studies are of little or no value because factors such as age, sex, level of physical activity and the non-specific effect of chronic disease are known to affect the level of steroid secretion. Certainly much more information should be sought regarding factors influencing the "normal" range, and the non-specific effect of debilitating illness.

Likewise, as Robinson has cautioned, the interpretation of the pattern of steroid excretion in the urine may prove misleading inasmuch as such values do not necessarily represent the functional status of the adrenal cortex or the material it is releasing into the blood stream. 10 Information as to changes in these steroids between the time they leave the adrenal and the time they are identified in the urine would be extremely important. Without proper evaluation of this physiological concept one might be led into an erroneous conclusion of an abnormal steroid production in what may actually constitute an abnormal systemic metabolism of the steroids before their metabolites appear in the urine. It is indeed possible that our present methodology for identification of these products is still too crude to identify and differentiate all the products that are released from the adrenal cortical cells into the adrenal vein. Determination of plasma steroid levels would be of some value in this regard, but, here again, it might not represent the entire picture.

It has been postulated that a relative adrenal insufficiency might result from an abnormally increased tissue hormone demand in this disease. In such individuals, the anterior pituitary stimulus, although increased, would not result in an increased plasma level of the hormone. Such an abnormality has been reported in patients with well established rheumatic fever. 11 In these patients, although the plasma corticotropin concentration is persistently elevated, the cortisone level remains below the normal. This pathophysiological state might be presumed to be due to adrenal cortex exhaustion possibly predicated on an increased tissue steroid utilization. That there might exist a similar condition in rheumatoid arthritis has been considered, but no confirmatory evidence has been forthcoming. Peterson measured the disappearance rate from the plasma of labeled compound F in several patients with this disease and although the majority of his subjects showed

⁸ Howard, R. P., Venning, E. H., and Fisk, G. H.: Rheumatoid arthritis; studies of adrenocortical and hypophyseal function and the effects thereon of testosterone and pregnenolone therapy, Canad. M.A.J. 63: 340, 1950.

^o Staub, P. L., Menthe, J. W., Nelson, S. S., and Cohn, H.: Excretion of 11-oxycorticosteroids in paraplegic and rheumatoid arthritis patients, J. Clin. Investigation 29: 349

Robinson, W. D.: Discussion of footnote 17, Ann. Rheumat. Dis 15: 71 (Mar.) 1956.
 Kelly, V. C.: Rationale for hormone therapy in rheumatic fever, Ann. N. York Acad.
 61: 369-376 (May 27) 1955.

disappearance rates within the predetermined normal, in some the rates were substantially increased.12 Further studies along these lines, taking into account the activity of the disease, would be of interest.

The adrenal response to corticotropin administration as measured by the urinary 17-hydroxysteroid and 17-ketosteroid excretion is considered an adequate test for determining the available functional reserve of the adrenal cortex. The results obtained when individuals with rheumatoid arthritis are subjected to such a test, have consistently compared favorably with those observed in normals.¹⁸ Even in those patients with subnormal pre-treatment levels of urinary 17-hydroxysteroid, excretion levels promptly return to normal after corticotropin administration. These findings would appear to indicate that in rheumatoid arthritis there is no intrinsic adrenal cortical insufficiency in that the adrenal cortex responds normally to exogenous

corticotropin stimulation.

Could the abnormality then be due to an easily exhausted mechanism for production of the steroids by the adrenal gland? However, repeated intravenous administration of corticotropin over long periods of time, even months, does not result in any perceptible alteration in the adrenal response. 18, 14 This is evidence that the adrenal cortex is not easily exhausted and that its reserve capacity is similar to that observed in normal individuals. There appears to be fairly good correlation between the dosage, urinary excretion of steroid metabolites, and clinical effect during prolonged administration of corticotropin in this disease state. These findings would appear to exclude an "exhaustion" of the adrenal cortex as a causative factor in rheumatoid arthritis.

Does the adrenal cortex secrete an abnormal steroid in rheumatoid arthritis and could this explain the bizarre symptomatology in this disease state? Dobriner, utilizing a laborious isolation method, has found the excretion of steroid hormone metabolites to be consistently at a low normal level in five patients with rheumatoid arthritis. 15 In addition, four of the five patients excreted a steroid, 17-hydroxypregnenolone, that has been previously encountered only in subjects with manifest adrenal dysfunction. Confirmatory evidence, however, has not been forthcoming.

Why then does cortisone give at least some temporary relief of symptoms in patients with rheumatoid arthritis? The present consensus as to the maximum dosage schedule recommended in this disease state approximates closely the estimated normal output of the adrenal cortex.16 With the known

Dobriner, K.: Symposium on steroids in experimental and clinical medicine, 1951,
 The Blakiston Company, Philadelphia, p. 130.
 Holley, H. L.: Recent advances in steroid therapy of rheumatoid arthritis, Mississippi Doctor 33: 257-259 (Feb.) 1956.

¹² Peterson, R. E., Wyngaorden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J.: The physiological disposition and metabolic fate of hydrocortisone in man, J. Clin. Investigation 37: 779-794, 1955.

Hill, S. R. and coworkers: Unpublished data.
 Fisher, F. K.: Corticotropin and cortisone in rheumatoid arthritis, Acta med.
 Scandinav. Suppl. 305: 137, 1955.

suppression of adrenal steroid production by administration of exogenous hormones, how can one explain why the same amount of hormones presumably produced by a normal adrenal gland produces therapeutic results? Such a fact would appear to offer support for the proponents of the concept that this is a deficiency state.

Recent work has demonstrated an alteration in the normal diurnal pattern of urinary steroid excretion in rheumatoid arthritis. 17 Investigations by Thorn and Laidlaw had previously found a remarkable consistency of such a pattern in the normal individual.¹⁸ This change in rate of excretion of steroid metabolites during the early morning hours, though fairly consistent, proved non-specific for the disease. However, the decreased excretion of urinary steroid metabolites can be correlated with the early morning exacerbation of muscular stiffness, so characteristic of rheumatoid arthritis. Recently there has been confirmatory work in this regard. Warren has measured the plasma corticoids in patients with rheumatoid arthritis and found an alteration of the expected diurnal pattern which could be correlated with the altered pattern of urinary steroid metabolite excretions. 19

In his hypothesis of the diseases of adaptation, which include rheumatoid arthritis, Selye contends that their pathogenic basis may be a disturbance in the ratio of mineralo- and gluco-corticoid production by the adrenal cortex, but confirmatory evidence of this imbalance has not been forthcoming. Recently Wilson analyzed the urine of two male subjects with rheumatoid arthritis for their steroid content and compared the results with those obtained from a normal male.20 The identification procedures revealed two polar metabolites, compound E and compound tetrahydro E to be present in the normal but absent in the urine of the arthritic patient. Five less polar steroid metabolites, still unidentified, were present in the urine obtained from the arthritic, but were absent in the normal control. It is interesting that after administration of corticotropin to the individual with arthritis the "abnormal" steroid metabolites diminished or disappeared, to be replaced by the metabolite pattern found in the normal. Further studies along this line are now in progress, but the results as yet are unavailable.

There appears to be increasing evidence that the anterior pituitary, under whose control the adrenal cortex secretes cortisone and cortisone-like materials, may be implicated in the etiology of this disease syndrome. However, here again, as in Addison's disease, patients with pituitary insufficiency such as results from a chromophobe adenoma do not have an increased incidence of arthritis. It is interesting to note, however, that in postpartum

 ¹⁷ Hill, S. R., Jr., Holley, H. L., Starnes, W. R., and Hibbett, L. L.: Studies on the diurnal pattern of urinary 17-hydroxycorticoid and 17-ketosteroid excretion in patients with rheumatoid arthritis, Ann. Rheumat. Dis. 15: 69-71 (March) 1956.
 18 Thorn, G. W., and Laidlaw, J. C.: Studies on the adrenal cortical response to stress in man, Tr. Am. Clin. and Climat. A. 65: 179, 1954.
 19 Warren, Joseph E.: Discussion of footnote 17, Ann. Rheumat. Dis. 15: 70 (March)

²⁰ Wilson, Hildegard: Discussion of footnote 17, Ann. Rheumat. Dis. 15: 70 (March) 1956.

pituitary deficiency, as described by Sheehan, the author states: "These patients are unduly liable to develop rheumatism in the knee," although no differentiation as to the type of arthritis is made. 21

Pearse observed in 9 of 10 autopsied patients with active rheumatoid arthritis and in one of three patients with lupus erythematosus, identical abnormalities of the cellular structure of the anterior pituitary.²² These changes consist of a selective degranulation of the mucoid cells (basophils, cyanophils) similar to that seen in Addison's disease; but not found in a series of 200 controls.

It could be theorized, then, that the apparent "steroid abnormality" observed by Wilson could conceivably be a result of the ineffectiveness of the endogenous corticotropin rather than the inability of the adrenal cortex to produce the normal complement of hormones.20 Peterson, in some preliminary studies, has found a diminished compound F synthesis by the adrenal cortex in individuals suffering from rheumatoid arthritis.28 Presumably this abnormality, too, might result from either a quantitative or qualitative abnormality of endogenous corticotropin production under whose influence the cortex synthesizes the 11, 17-oxygenated steroids. It is thought that the alteration in the diurnal steroid excretion pattern as observed by Hill and Warren likewise may not reflect variations in the intermediary metabolism or excretion of adrenal cortical steroids, but a change in the pituitary-adrenal or hypothalamic-pituitary-adrenal secretory mechanism. This information represents a new approach in unraveling the mystery; however, further studies along these lines will be required to determine whether this phenomenon is specific for rheumatoid arthritis.

It is at present impossible to ascertain whether the apparent pathophysiological alteration in anterior pituitary function is a cause of the disease or a result of the chronic disease state or whether it may be merely involved in the perpetuation of the symptoms. Certainly further studies concerning the effect of chronic disease, sex, age, and degree of activity on the anterior pituitary gland function are indicated. It will be from such investigations that a more definitive analysis can be made of the rôle played by the pituitary-adrenal cortex interrelationship in the etiology of this disease.

HOWARD L. HOLLEY, M.D.

28 Peterson, R. E.: Personal communication.

 ²¹ Sheehan, H. L.: Simmonds' disease due to postpartum necrosis of the anterior pituitary, Quart. J. Med. 8: 277-309 (Oct.) 1939.
 ²² Pearse, A. G. E.: The hypophysis in rheumatoid arthritis, Lancet 1: 954 (May 20), 1950.

REVIEWS

The Haemolytic Anaemias, Congenital and Acquired. By J. V. DACIE, M.D. (Lond.), M.R.C.P. (Lond.); Reader in Haematology, Department of Pathology, Postgraduate Medical School of London. 525 pages; 14.5 × 22 cm. Grune and Stratton, Inc., New York. 1954. Price, \$7.50.

It is a real pleasure to follow the author through his learned and comprehensive discussion of the hemolytic anemias, a subject about which he is one of the world's foremost authorities. Dr. Dacie has drawn heavily from his extensive personal experiences in this field and, where pertinent, reviews the literature of the past 15 years in summarizing present knowledge regarding etiology, symptomatology, diag-

nosis, and therapy of the hemolytic anemias.

The book begins with a brief survey of the mechanisms of increased hemolysis and the methods in which hemolytic anemias may best be investigated. The remaining 17 chapters are devoted to the congenital hemolytic anemias, acquired hemolytic anemias, hemolytic anemias due to drugs, chemicals, and infections, a section on paroxysmal nocturnal hemoglobinuria, hemolytic disease of the newborn, and an excellent and most useful section entitled, "Haematological Techniques Useful in the Investigation of Haemolytic Anaemias."

It is unfortunate that the print of the pages is so small since it makes for difficult reading. The addition of a number of illustrative charts and diagrams as well as the excellent bibliographies at the end of each chapter, all go to increase the

value of the text.

It is not often an authoritative volume written by a man so well versed in his field appears on the medical horizon. Certainly Dr. Dacie's contribution to the literature of the hemolytic anemias should be of interest to all internists.

Atlas der klinischen Hämatologie und Cytologie (in German, English, French and Spanish). By Ludwig Heilmeyer and Herbert Begemann. In 2 volumes: 383 pages; 20.5 × 28 cm. Springer-Verlag, Berlin. 1955. Price, Ganzleinen DM 195,—(both volumes).

This atlas is a most impressive collection of colored drawings of the microscopic appearance of peripheral blood and bone marrow, as well as certain other types of cells and tissues. The work is published in two volumes; one contains the entire 261 plates, each labeled briefly in four languages, and a subject index; the second contains the text, written in four sections-each a different language-and the same subject index. The separation of plates from text makes the handling of the two books simultaneously a bit cumbersome, and especially so since the text is swollen by the same material presented in four languages. However, this separation allows for ample description of the plates, as well as material concerning technic of obtaining specimens, staining, and some clinical information.

Included in these volumes are illustrations of the normal peripheral blood and bone marrow (each cellular element is pictured separately and then the tissue as a whole is shown) a brief section on the anemias, and a long section on the leukemias. An interesting group of plates is devoted to spleen and lymph node puncture specimens. There is a short portion devoted to liver biopsy (material is both smeared and sectioned) and a few pages of cytology of various other organ punctures (thyroid, prostate). Twenty-one plates are shown to picture "tumor punctures," although it is recognized that the site of origin of a neoplasm is rarely determined in this manner. The cytology of body fluids (including vaginal smears) is pictured next and, finally, the more common parasites are shown.

The translation of the text from the original German into English is basically very readable. However, the terminology (particularly in the sections dealing with the blood) in some instances differs from that generally used in this country. The authors are dogmatic in many areas where there is still room for discussion, and some of their statements are definitely misleading. (The section on the acute leukemias is an example.) Nevertheless, the high quality of the illustrations make this work an asset to any student, practitioner, or teacher interested in cytology, and the text is particularly useful in its descriptive aspects.

ALICE BAND, M.D.

Cardiac Pressures and Pulses: A Manual of Right and Left Heart Catheterization. By Aldo A. Luisada, M.D., Associate Professor of Medicine, The Chicago Medical School, and Chi Kong Liu, M.D., Instructor of Medicine, The Chicago Medical School. Grune & Stratton, Inc., New York 16, N. Y. 1956. Price, \$6.00.

Cardiac catheterization is being more widely employed as a routine procedure for the diagnosis and evaluation of acquired and congenital heart disease. The authors of this manual discuss both right and left heart catheterization. They describe in some detail the cardiac cycle, technic of catheterization, normal and abnormal pressures, and pressure patterns, artifacts and formulas used in cardiac catheterization. The manual is profusely illustrated and well edited. The cross references in the index are particularly valuable; the figures are placed opposite the relevant text and this allows convenient study of the material. In a text such as this one may differ with details of description and illustration on the basis of one's own experience. This manual should prove of considerable value to all students interested in cardiology. Cardiologists should find it of value as a handy reference book.

Die L. S.

Klinische Fehldiagnosen. By Prof. Dr. M. BÜRGER. 550 pages; 17.5 × 24.5 cm. George Thieme Verlag, Stuttgart. 1954. Price, \$14.15.

This second edition of a treatise on diagnostic errors by a famous German teacher, clinician and investigator, is a valuable addition to a medical library. Although the unearthing of new facts, knowledge and concepts is proceeding at a tremendous speed, the teaching of the medical art and science continues to have as its main purpose the

prevention, diagnosis and healing of disease.

Professor Bürger's accumulation and critical presentation and discussion may be likened to a systematic presentation of cases from clinico-pathological conferences, to the Cabot series as published by the New England Journal, etc. Although some professors of medicine in their esoteric remoteness from the practice of medicine look with disdain and suspicion at such a comparative mode of teaching, it is going to retain its importance altered only by the addition of newer facts and ideas. The author presents a group of cases, their histories, clinical findings and the wrong and correct diagnoses. The lessons to be learned from the committed errors are then ably discussed and summarized for each organ system. Its purpose is more to teach clinical thinking than to present a complete discussion of the topic. One cannot always agree with all statements, conclusions and the development of thought. The art of clinical medicine allows for differences in interpretation.

The text is well written, thought, presented, and discussed. Many illustrations are well chosen, others could well be replaced by better ones in the next edition (particularly the electrocardiograms). Reproductions and printing are excellent.

ARTHUR GRISHMAN, M.D.

Klinische Vektorkardiographie. Band 15. Kreislauf-Bücherei, Herausgegeben in Verbindung mit der Deutschen Gesellschaft für Kreislaufforschung. By Univ. Dozent Dr. Rudolph Wenger. 163 pages; 15.5 × 22.5 cm. Verlag von Dr. Dietrich Steinkopff, Darmstadt. 1956. Price, brosch. DM 24.-; geb. DM 26.-

The introduction to clinical vectorcardiography is preceded by a clear and concise picture of the various problems entailed, conceptional as well as technical. A his-

torical description of the electrometer of Waller and of the string galvanometer of Einthoven is followed by a very brief presentation of the very basic electronics involved in amplifier design. The historical development of vectorconcept and vectorcardiography is accurately detailed. The descriptive and clinical part of the monograph contains a great deal of valuable and often new information. "Dérouler" presentation of vectors, however, is not a technic best suited for vectorcardiography and never became popular elsewhere than the laboratories of Hollmann and Milavanovich. In some chapters exception may be taken to some of the conclusions: it is most doubtful that left bundle branch block permits the detection of an associated myocardial infarction. The basic thought underlying the vectorconcept would preclude one's ability to do so.

The text is well written, the presentation is clear throughout. The illustrations are not always very distinct but most of them present their point well. Diagrams and photographs of models are helpful and well executed. Printing and reproductions are of high quality.

ARTHUR GRISHMAN, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Advances in Internal Medicine. Volume VIII, 1956. Editors: WILLIAM DOCK, M.D., State University of New York College of Medicine at New York City; and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. 366 pages; 23.5 × 15.5 cm. 1956. The Year Book Publishers, Inc., Chicago. Price, \$9.00.
- Atlas d'Électrocardiographie avec des Notions de Vectorcardiographie à l'Usage du Médecin Praticien et de l'Étudiant. 4th Ed. By V. Fattorusso and O. Ritter. 295 pages; 17.5 × 25 cm. 1956. Masson et Cie, Paris. Price, 3.200 fr.
- Borderlands of the Normal and Early Pathologic in Skeletal Roentgenology. 10th Ed. By Prof. Dr. Alban Köhler. Tenth Edition Completely Revised with Reference to Illustrations and to Text by Dozent Dr. E. A. Zimmer; English Translation Arranged and Edited by James T. Case, M.D., D.M.R.E. (Cambridge), Professor Emeritus of Radiology, Northwestern University Medical School, Chicago, etc. 723 pages; 26.5 × 17 cm. 1956. Grune & Stratton, Inc., New York. Price, \$24.50.
- Cardiac Pressures and Pulses: A Manual of Right and Left Heart Catheterization. By Aldo A. Luisada, M.D., Associate Professor of Medicine, The Chicago Medical School, etc.; and Chi Kong Liu, M.D., Instructor of Medicine, The Chicago Medical School, etc. 116 pages; 26 × 17.5 cm. 1956. Grune & Stratton, Inc., New York. Price, \$6.00.
- Clinical Hematology. 4th Ed. By MAXWELL M. WINTROBE, M.D., Ph.D., Professor and Head, Department of Medicine and Director Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah, College of Medicine, Salt Lake City, Utah, etc. 1,184 pages; 24 × 16 cm. 1956. Lea & Febiger, Philadelphia. Price, \$15.00.
- Composting: Sanitary Disposal and Reclamation of Organic Wastes. World Health Organization Monograph Series No. 31. By Harold B. Gotaas, Professor of Sanitary Engineering, Department of Engineering, University of California, Berkeley, Calif., USA. 205 pages; 24 × 16 cm. 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$5.00.

- Cytology of the Blood and Blood-Forming Organs. By MARCEL BESSIS, Director of Research Laboratory, Centre National de Transfusion Sanguine, Paris, France; translated by Eric Ponder, The Nassau Hospital, Mineola, New York. 629 pages; 26 × 17.5 cm. 1956. Grune & Stratton, New York. Price, \$22.00.
- The Doctor in Personal Injury Cases. By Harold A. Liebenson, Member of Illinois, Chicago and American Bar Associations. 123 pages; 18.5 × 12 cm. 1956. The Year Book Publishers, Inc., Chicago. Price, \$4.00.
- Endogenous Uveitis. By Alan C. Woods, M.D., Professor Emeritus of Ophthalmology, the Johns Hopkins University School of Medicine and Emeritus Ophthalmologist-in-Chief of the Johns Hopkins Hospital; with illustrations by Annette Smith Burgess, Instructor in Art as Applied to Medicine, the Johns Hopkins University School of Medicine. 303 pages; 26 × 18 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, \$12.50.
- Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel: Third Report. World Health Organization Technical Report Series No. 109. 19 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Expert Committee on Trachoma: Second Report. World Health Organization Technical Report Series No. 106. 20 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Food Hygiene: Fourth Report of the Expert Committee on Environmental Sanitation. World Health Organization Technical Report Series No. 104. 28 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- A History of the Therapy of Tuberculosis and the Case of Frederic Chopin. Logan Clendening Lectures on the History and Philosophy of Medicine, Sixth Series. By ESMOND R. Long, M.D., Director of the Henry Phipps Institute, University of Pennsylvania, etc. 71 pages; 21.5 × 14 cm. 1956. University of Kansas Press, Lawrence. Price, \$2.00.
- Hutchison's Food and the Principles of Dietetics. 11th Ed. Revised by V. H. Mottram, M.A. (Cant.), Sometime Fellow of Trinity College, Cambridge, etc.; and George Graham, M.A., M.D. (Cant.), F.R.C.P. (Lond.), Consulting Physician to St. Bartholomew's Hospital. 630 pages; 22.5 × 14 cm. 1956. The Williams & Wilkins Company, Baltimore. Price \$8.25.
- Infant Metabolism: Proceedings of the World Health Organization's Seminars Held at Leyden and Stockholm in October-November, 1950. Conducted by Evert Gorter, Professor of Pediatrics, University of Leyden Medical College, Leyden; S. Z. Levine, Professor of Pediatrics, Cornell University Medical College, New York; and Arvid Wallgren, Professor of Pediatrics, Caroline Institute, Stockholm; edited by I. Herbert Scheinberg, Associate Professor of Medicine, Albert Einstein College of Medicine, Yeshiva University, New York. 435 pages; 23.5 × 15.5 cm. 1956. The Macmillan Company, New York. Price, \$8.00.
- Malaria Conference for the Western Pacific and South-east Asia Regions (Second Asian Malaria Conference), Baguio, Philippines, 15-24 November 1954: Report. World Health Organization Technical Report Series No. 103. 44 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in

- U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Meditations on Medicine and Medical Education, Past and Present. By I. SNAPPER, M.D. 138 pages; 22 × 14.5 cm. 1956. Grune & Stratton, New York. Price, \$3.75.
- The Morphology of Human Blood Cells. By L. W. Diggs, M.A., M.D., Professor of Medicine and Director of Medical Laboratories, University of Tennessee and City of Memphis Hospitals, etc.; Dorothy Sturm, Instructor, Memphis Academy of Arts; and Ann Bell, B.A., Instructor in Medicine, University of Tennessee. 181 pages; 28 × 21 cm. (loose-leaf). 1956. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Physical Diagnosis. 5th Ed. By RALPH H. MAJOR, M.D., Professor of Medicine and of the History of Medicine, The University of Kansas; and MAHLON H. Delp, M.D., Professor of Medicine, The University of Kansas. 358 pages; 26 × 17 cm. 1956. W. B. Saunders Company, Philadelphia. Price, \$7.00.
- Progress in Hematology. Volume 1, 1956. Edited by Leandro M. Tocantins, M.D., with 27 contributors. 336 pages; 26 × 18 cm. 1956. Grune & Stratton, New York. Price, \$9.75.
- The Recovery Room: Immediate Postoperative Management. By Max S. Sadove, M.D., Professor of Surgery (Anesth.) and Head, Division of Anesthesiology, University of Illinois College of Medicine and the Research and Educational Hospitals; and James H. Cross, M.D., Clinical Assistant Professor in Surgery, University of Illinois College of Medicine; with contributions by 24 authorities. 597 pages; 24 × 16 cm. 1956. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Some Clinical Applications of Electroneurophysiology, Especially Electrodiagnosis and Electromyography. Volume I of Physical Medicine Library. Edited by Sidney Licht, M.D., Honorary Member, British Association of Physical Medicine, Danish Society of Physical Medicine, and the French National Society of Physical Medicine. 272 pages; 23.5 × 15.5 cm. 1956. Elizabeth Licht, Publisher, New Haven, Connecticut. Price, \$10.00.
- Synopsis of Gynecology, Based on the Textbook, Diseases of Women. 4th Ed. By ROBERT JAMES CROSSEN, M.D., F.A.C.S., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. 255 pages; 20 × 13 cm. 1956. The C. V. Mosby Company, St. Louis. Price, \$5.25.
- A Text Book of Pathology. 8th Ed. By E. T. Bell, M.D., Emeritus Professor of Pathology in the University of Minnesota, Minneapolis, Minn. Contributors: B. J. Clawson, M.D., Emeritus Professor of Pathology in the University of Minnesota; and J. S. McCartney, M.D., Professor of Pathology in the University of Minnesota. 1,028 pages; 24 × 15.5 cm. 1956. Lea & Febiger, Philadelphia. Price, \$14.50.
- Treatment of Heart Disease: A Clinical Physiologic Approach. By Harry Gross, M.D., F.A.C.P., Attending Physician, the Montefiore Hospital, etc.; and Abraham Jezer, M.D., Attending Physician, the Montefiore Hospital, etc. 549 pages; 26 × 17 cm. 1956. W. B. Saunders Company, Philadelphia. Price, \$13.00.
- Treatment of Migraine. New England Journal of Medicine Medical Progress Series. By John R. Graham, M.D., Chief, Medical Service, Faulkner Hospital, Boston, etc. 149 pages; 19.5 × 12.5 cm. 1956. Little, Brown and Company, Boston. Price, \$4.00.

COLLEGE NEWS NOTES

SUBMISSION OF TITLES FOR A.C.P. 1957 SESSION

The Committee on Educational Policy of the Board of Regents has suggested that the Fellows and Associates of the College be invited to submit titles and abstracts (not to exceed 200 words) of papers to be considered for the Annual Session of the American College of Physicians at Boston, Mass., April 8-12, 1957. Consequently, all Fellows and Associates are invited to submit titles and abstracts to the President, Dr. Walter L. Palmer, 950 E. 59th St., Chicago 37, Ill., prior to Oct. 1, 1956. Presumably, it will be possible to place on the program of the 1957 Session at Boston, only a small portion of the papers submitted. It is hoped, however, that the plan will bring to light many subjects and speakers who might be overlooked, and also that some information will be afforded regarding current interests. Suggestions may thus arise for symposia, panel discussions, morning lectures, clinics, and the afternoon sessions.

NEW LIFE MEMBERS

The College acknowledges with pleasure the following Fellows as Life Members:

Dr. Ralph E. Homann, Jr., Los Angeles, Calif.

Dr. Harvey C. Schneider, Buffalo, N. Y.

Dr. Ernest W. Shaw, La Mesa, Calif.

Dr. Franklin Moosnick, Lexington, Ky.

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College expresses its appreciation to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

James L. McCartney, M.D., F.A.C.P., Garden City, N. Y., Understanding Human Behavior, published by the Vantage Press, N. Y., June, 1956.

Julius H. Comroe, Jr., M.D., F.A.C.P., Philadelphia, Pa., in collaboration with Robert E. Forster, II, M.D., Arthur B. Dubois, M.D., William A. Briscoe, M.D., and Elizabeth Carlsen, A.B., The Lung-Clinical Physiology and Pulmonary Function Tests, published by The Year Book Publishers, Inc., Chicago, June, 1956.

Elmer G. Wakefield, M.D., F.A.C.P., Rochester, Minn., Clinical Diagnosis, published by Appleton-Century-Crofts, Inc., N. Y., June, 1956.

AUTUMN A.C.P. COMMITTEE MEETINGS

The meetings of the Board of Regents and Committees of the College will be held on Nov. 8-11, 1956, at College Headquarters in Philadelphia. The Committee on Credentials will meet Nov. 8-9, and the Board of Regents, Nov. 10-11.

Proposals for advancement to Fellowship and/or new members for action at these meetings, must be received at College Headquarters 60 days in advance of these dates. Governors may require that proposals be in their hands 90 days before the meetings.

The Committee on Credentials will hold a meeting at Philadelphia, March 9-10, 1957, and at Boston, April 5-6, immediately preceding the Board of Regents meeting

on Apr. 6-7, 1957.

AMERICAN COLLEGE OF PHYSICIANS RECEIVES RESEARCH GRANT

A research grant of \$43,100.00 has been awarded the American College of Physicians for the period September 1, 1956, through August 31, 1957, by the Department of Health, Education, and Welfare of the Public Health Service in furtherance of its project to evaluate internal medicine in hospitals. This project, "to establish a minimal standard of quality and efficiency of the practice of internal medicine in hospitals," was initiated in early 1956, by the College's Committee on Criteria for Hospital Accreditation, under the chairmanship of Dr. Arthur R. Colwell, Sr., F.A.C.P., Chicago.

The Director of the study is Dr. Marion A. Blankenhorn, F.A.C.P., Cincinnati, who is devoting his full time to the project. A pilot study of approximately one hundred representative hospitals is being conducted by observing practice methods with particular reference to internal medicine. Twenty or more mature and responsible physicians are being sent to selected sites to observe current practices; to record the type of patient admitted to a hospital, the diseases, length of stay and the means employed for diagnosis and treatment; and to classify findings—viz., approved, provisionally approved, and not approved. A search is being directed to the mechanics of internal medicine as practiced in a wide variety of circumstances (large, small, voluntary, tax-supported, private, teaching or non-teaching), especially the use of clinical laboratory devices; habits of consultation, and use of ancillary skills such as physical medicine, rehabilitation, preventive medicine and others. Such observations and records will be edited by the Director and reviewed by the Committee on Criteria.

Whereas appraisal of medical care will be the primary objective, information will be gathered also regarding internships and residencies in Medicine where such programs exist. Close liaison will be maintained with the Council on Medical Education and Hospitals of the American Medical Association and appropriate committees in the Association of American Medical Colleges. The Committee does not suggest that this pilot study shall substitute for any part of the present programs of the Joint Commission on Accreditation of Hospitals or the Council on Medical Education and Hospitals of the A.M.A., but will proceed parallel to the existing programs of both, probably leading to some revision in their Internal Medicine policies in the future.

SCHEDULE OF COMING A.C.P. REGIONAL MEETINGS

Date	Territory	Governor			
Sept. 7-8	NEW ENGLAND, (Que., Me., Vt., N. H., Mass., Conn., R. I.), Burlington, Vt.	Elbridge E. Johnston, M.D. Chairman			
Sept. 29	WEST VIRGINIA, Charleston	Paul H. Revercomb, M.D.			
Oct. 16	NEW MEXICO, Albuquerque	Robert Friedenberg, M.D.			
Oct. 19	WESTERN NEW YORK, Albany	John H. Talbott, M.D.			
Oct. 19-21	SOUTHEASTERN, (Ala., Ga., S. C., Fla., Cuba), Nassau, Bahama Islands	William C. Blake, M.D., Chairman			
Oct. 20	ARKANSAS-OKLAHOMA, Tulsa, Okla.	Bert F. Keltz, M.D., Chair- man			

Oct. 27	MIDWEST, (Minn., Wis., Iowa, Ill., Ind.), Minneapolis, Minn.	Wesley W. Spink, M.D., Chairman
Nov. 7	NEW JERSEY, Newark	Edward C. Klein, Jr., M.D.
Nov. 16-17	MONTANA-WYOMING, Great Falls, Mont.	Harold W. Gregg, M.D., Chairman
Dec. 1	MICHIGAN, Ann Arbor	H. Marvin Pollard, M.D.
Dec. 1	KENTUCKY-TENNESSEE, Nashville, Tenn.	Rudolph H. Kampmeier, M.D., Chairman
Dec. 6	NORTH CAROLINA, Chapel Hill	Elbert L. Persons, M.D.

THE RESIDENCY REVOLVING LOAN FUND OF THE AMERICAN COLLEGE OF PHYSICIANS

The College has established a Revolving Loan Fund to aid young physicians planning a future career in internal medicine or specialties allied thereto, to pursue adequate graduate training as full-time residents, research assistants, junior instructors, and/or fellows in accredited institutions, which training might otherwise not be available to them because of financial needs. The Committee may give some priority to candidates anticipating careers in academic medicine, although that is not a requirement. The limit of each loan is \$1,000.00. Loans may be made for varying periods of time, up to a maximum of ten years, but may be repaid in part or in full at any time. No interest is charged for the first two years of the loan; thereafter, simple interest shall be charged at the rate of 3% per annum, payable annually.

Applications are made direct on the official forms supplied by the College, 4200 Pine St.. Philadelphia 4, Pa.

The capital of the Loan Fund currently is \$40,000.00, and it will be increased \$20,000.00 per annum to build up to a total fund of \$100,000.00.

FELLOWSHIPS AND SCHOLARSHIPS OFFERED BY THE AMERICAN COLLEGE OF PHYSICIANS

Research Fellowships. There is a limited number of six Research Fellowships in Medicine granted annually by the College. All awards have been made for 1956, and applications are now being received for the period starting July 1, 1957. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences, or in the application of these sciences to clinical investigation. The stipend varies from \$3,300.00 to \$5,000.00, depending on the number of dependents. Application forms must be filed in duplicate not later than Oct. 1, 1956, for fellowships beginning July 1, 1957. Announcement of the awards will be made during November, 1956. Full details and application forms may be obtained from the Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa.

Traveling Scholarships. The Traveling Scholarships of the American College of Physicians are aimed primarily for the assistance of Associates of the College to enable them to spend a month, more or less, as visiting fellows to some institution, or institutions, for observation and postgraduate study. The Committee on Scholarships of the College can readily facilitate opportunities for these fellowships at outstanding institutions where a month's observation, contact and study will be an exceptional inspiration and a practical source of training.

The College has two A. Blaine Brower Traveling Scholarships, one Elizabeth Archbold Bowes Traveling Scholarship (restricted to Associates from Canada), and

one Willard O. Thompson Memorial Traveling Scholarship (particularly aimed at the specialty of Endocrinology). Applications, procurable from the Executive Secretary's office, must be filed by Oct. 1, for the period starting January, 1957.

A.C.P. COMMITTEE ON SPECIAL FUND RAISING

At a meeting of the Board of Regents at Los Angeles, Calif., April 20, 1956, a Committee of Regents, consisting of Dr. George F. Strong, Chairman, Vancouver, Dr. Philip S. Hench, Rochester, Dr. Joseph D. McCarthy, Omaha, and Dr. Cyrus C. Sturgis, Ann Arbor, was appointed for the purpose of exploring availability of funds for two specific purposes, to wit:

- A permanent fund from which distinguished foreign medical guests may be financed for presentations before the Annual Sessions of the College;
- (2) To enable the College to bring to America, or Canada, recent graduates of foreign medical schools for one year of postgraduate training.

The American College of Physicians has for some years had a policy for the furtherance of closer good will and coöperation between the College and other comparable national medical groups. It has been the custom to invite distinguished medical authorities from other countries to attend the Annual Sessions of the College as guest lecturers. The Lilly Research Laboratories already have on numerous occasions underwritten the travel expenses each year of at least one such foreign guest.

The new Committee will explore ways and means to raise funds through foundations and/or commercial institutions to carry out the above projects.

A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Louis N. Katz, M.D., F.A.C.P., Richard Langendorf, M.D., F.A.C.P., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m., December 3 to 7, 1956.

Further information and a copy of the lecture schedule may be obtained from Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

The 24th Annual Assembly of the Omaha Mid-West Clinical Society will be held Oct. 29-Nov. 1, 1956, at the Fontenelle Hotel, Omaha, Nebraska.

The program will consist of two Sessions: A morning Session composed of motion pictures, Morning Lectures and General Sessions, with a guest lecturer. The Afternoon Sessions will have a Panel consisting of a moderator and four panelists who will present short dissertations on various subjects; a general discussion will follow. In addition to the Panels, there will be General Sessions with visiting lecturers.

During the noon and evening intermissions, there will be discussions on specific topics, led by moderators. The Conference will have many Scientific and Technical Exhibits which should be of interest to all in attendance.

Members from the College participating in the Annual Assembly are: Maurice C. Howard, M.D., F.A.C.P., Maurice L. Pepper, M.D., (Associate), Charles M. Root, M.D., (Associate), Harold N. Neu, M.D., F.A.C.P., Eugene E. Simmons, M.D., F.A.C.P., Edmond M. Walsh, M.D., F.A.C.P., GOVERNOR, A.C.P. FOR NE-BRASKA, and George W. Loomis, M.D., (Associate), all of Omaha, Nebraska;

Chester S. Keefer, M.D., F.A.C.P., Boston, Mass., and George C. Griffith, M.D., F.A.C.P., GOVERNOR, A.C.P., FOR SOUTHERN CALIFORNIA.

Anyone desiring additional information about the Annual Assembly may write to Mrs. Anne K. Ramsey, Executive Secretary, Omaha Mid-West Clinical Society, 1031 Medical Arts Building, Omaha 2, Nebraska.

LIFE INSURANCE MEDICAL RESEARCH FUND

Research Fellowships and Grants

Applications for awards available July 1, 1957, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 15, 1956. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend \$3,800, with allowances for dependents and necessary travel. (2) Grants to institutions in aid of research on cardiovascular problems, until November 1, 1956. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Approximately \$1,000,000 will be available for the two types of award. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

MEAD JOHNSON GRADUATE RESIDENCY SCHOLARSHIPS

There are five such Scholarships available through the College, financed by Mead Johnson & Company. They provide \$1,000.00 each, annually. Recipients shall be individuals who intend to practice Internal Medicine, who appear to possess the attributes for success in that specialty, and who need some help to attain their goal of adequate education in Internal Medicine. The first awards available will start July 1, 1957. Application forms may be obtained through the Executive Secretary's Office of the College. One condition of these Scholarships is that the candidate be nominated by the College Governor for the state, province or territory in which he is located. The Executive Secretary will furnish the name and address of the appropriate Governor to each individual who desires to make application. Scholarships begin on July 1, and extend for one year. Applications must be filed by Oct. 1, 1956.

AMERICAN MEDICAL ASSOCIATION HONORS DR. BIERRING

Dr. Walter L. Bierring, M.A.C.P., Des Moines, Iowa, was selected by the House of Delegates of the American Medical Association at Chicago on June 11, to receive the Distinguished Service Medal. Dr. Bierring is a past President of the American Medical Association, of the Iowa State Medical Society, and of the Johnson County and Polk County Medical Societies in Iowa. He was for many years a Regent and member of various Committees of the American College of Physicians, and he was the first Secretary of the American Board of Internal Medicine. Currently, he is President of Alpha Omega Alpha Honorary Medical Society.

The Gold Medal and a citation were conferred upon Dr. Bierring at ceremonies in the Civic Opera House in Chicago, on June 12, when Dr. Dwight Murray of Napa, California, was inaugurated as President of the Association. The award was made in recognition of Dr. Bierring's achievements in public health and for his experience in medical examining board work.

ENCYCLOPEDIA BRITANNICA COMMISSIONS DR. EDWARD J. VAN LIERE

The Encyclopedia Britannica bestowed an honor on Dr. Edward J. Van Liere, F.A.C.P., Morgantown, W. Va., Dean and Professor of Physiology, West Virginia University School of Medicine, (Morgantown), when they commissioned him to write an article on Hypoxia, for the forthcoming edition of the Encyclopedia Britannica.

Dean Van Liere has done a great deal of research in the field of Hypoxia (anoxia). The last authority for the Encyclopedia was Sir Joseph Barcroft, the celebrated English physiologist, of Cambridge University, who wrote on the subject more than a quarter century ago. Dean Van Liere, one of the world's foremost authorities on anoxia, has written two books on the subject, namely, "Anoxia: Its Effect on the Body," and "Acclimatization to Low Oxygen Tension."

DR. ARTHUR S. ABRAMSON RECEIVES PRESIDENT'S TROPHY

Dr. Arthur S. Abramson, F.A.C.P., Professor and Chairman, Department of Rehabilitation, Albert Einstein College of Medicine, Yeshiva University, was presented the 1955 President's Trophy, which is awarded annually by the President's Committee on Employment of the Physically Handicapped. The presentation was made May 17, by Vice President of the United States, Richard M. Nixon, at the Annual Meeting of the Committee, in the Departmental Auditorium, Washington, D. C.

Dr. Abramson was selected "for the great inspirational example of rehabilitation that he represents, for the outstanding contribution that he is making to restoration of seriously handicapped persons to usefulness in the field of medicine and rehabilitation and for the leadership he has provided toward returning the disabled to independent living."

ECG TEST BOOK ISSUED BY HEART ASSOCIATION

The American Heart Association has announced the issuance of a two-volume "Electrocardiographic Test Book." The volumes are designed for teaching electrocardiography in medical schools and for postgraduate study by physicians. The books are edited by Travis W. Winsor, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Included in the first volume of the test book are 119 electrocardiograms, each of which is accompanied by several pertinent questions. There is also a section containing 230 general questions on electrocardiography and an index which includes a table of normal values. The second volume contains interpretations and discussions of the electrocardiograms and answers to the questions.

The "ECG Test Book" is the result of a two-year project commissioned by the Heart Association's Committee on Professional Education. Dr. Winsor was assisted in the preparation of the volumes by 34 leading authorities in the field of electrocardiography. These physicians reviewed the work and many of their suggestions were incorporated into the final text.

Copies of the "ECG Test Book" are available from the American Heart Association, 44 E. 23 St., New York 10, N. Y., at a cost of \$5.00 per set.

Two Members Receive Grants from National Vitamin Foundation

The National Vitamin Foundation, Inc., announced twelve new grants for a total of \$84,295.20, to American universities throughout the country, to augment the

extensive program of clinical and laboratory research in the fields of vitamins and nutrition. Two members of the College received grants under this program: Robert W. Hillman, M.D., (Associate), Associate Professor of Environmental Medicine and Community Health, State University of New York College of Medicine at New York City, received \$33,463.20, for the study of increased pyridoxine requirements in pregnancy; George W. James, III, M.D., (Associate), Associate Professor of Medicine, Medical College of Virginia, (Richmond), and Lynn D. Abbott, Jr., M.D., also from the Medical College of Virginia, received \$6,800, for studies of the vitamin B₁₂ growth activity of P. stipitata in human leukemia.

The National Vitamin Foundation gives grants-in-aid for research semiannually throughout the United States and abroad. These grants became effective July 1, 1956.

DR. HENRY C. SWEANY RECEIVES A.C.C.P. COLLEGE MEDAL

The American College of Chest Physicians, at its 22nd Annual Meeting, held June 6-10, at Chicago, Ill., presented Dr. Henry C. Sweany, F.A.C.P., the College Medal, for his outstanding contributions in the field of chest pathology.

Dr. Sweany is Director of Research, Pathology and Allied Sciences, Missouri State Sanatorium, (Mt. Vernon), and Associate Editor of the West Virginia Medical Journal. Among the newly elected officers of the American College of Chest Physicians for the year 1956-57 are:

President	Herman J. Moersch, M.D., F.A.C.P., Rochester, Minn.
President-Elect	Burgess L. Gordon, M.D., F.A.C.P., Philadelphia, Pa.
First Vice President	Donald R. McKay, M.D., F.A.C.P., Buffalo, N. Y.
Chairman, Board of Regents	John F. Briggs, M.D., F.A.C.P., St. Paul, Minn.

DR. RICHARD A. KERN GIVEN TESTIMONIAL DINNER

Dr. Richard A. Kern, F.A.C.P., President-Elect, A.C.P., was given a testimonial dinner June 19, by the Medical Staff and Heads of the Departments of Temple University Medical Center, in recognition of his outstanding services to Temple University Medical School.

Dr. Kern is a retired Rear Admiral in the U. S. Navy Medical Corps, with military service in World Wars I and II. He has been Professor of Medicine and Head of the Department of Medicine at Temple University Medical School, since 1946.

Dr. Walter L. Palmer, F.A.C.P., President, A.C.P., was honored June 10, when 150 of his friends and associates gathered in the home of Dr. and Mrs. Joseph B. Kirsner, F.A.C.P., of Chicago, and presented him with a bound volume of letters from former teachers, fellows and colleagues. A special feature of the occasion was the gift from seven members on the Gastro-intestinal Staff of the Hospital Obrero, (Lima, Peru), of a box of lignum vitae, covered with a piece of rare Incan tapestry.

The occasion was also in celebration of Dr. Palmer's 60th birthday, and in recognition of his election to the Presidency of the American College of Physicians.

Dr. Hugh R. Leavell, F.A.C.P., Professor of Public Health Practice and Head of the Department, Harvard School of Public Health, has taken a year's leave of absence to serve as Advisor to the Government of India, on problems of community sanitation and child and maternal health. Dr. Leavell will help organize a program

for training Indian health workers and on the evaluation of ways in which the cooperation of Indian villagers can best be obtained in community health projects. Dr. Leavell.will work through public health training centers near New Delhi, Calcutta and Madras. The program is being sponsored by the Ford Foundation through their grants to the Indian Government.

At the Annual Meeting of the Connecticut State Medical Society, Dr. Ralph T. Ogden, F.A.C.P., Hartford, assumed the duties as President, and Dr. W. Bradford Walker, F.A.C.P., Cornwall, was elected President-Elect, for the year 1957-58. Other newly elected officers are: Dr. Carl E. Johnson, New Haven, First Vice President; Dr. Otto G. Wiedman, F.A.C.P., Hartford, Second Vice President; Dr. Frank H. Couch, Cromwell, Treasurer; and Dr. Creighton Barker, New Haven, was re-elected Executive Secretary.

At the 22nd Annual Session of the Postgraduate Medical Assembly of South Texas, held July 16-18, at Houston, Drs. George C. Andrews, Jr., F.A.C.P., Professor of Clinical Dermatology, Columbia University College of Physicians and Surgeons; Eugene B. Ferris, Jr., F.A.C.P., Professor of Medicine and Chairman of the Department, Emory University School of Medicine, (Atlanta, Ga.); and R. Wayne Rundles, F.A.C.P., Associate Professor of Medicine, Duke University School of Medicine, (Durham, N. C.), gave courses in their respective fields.

Dr. Horacio Abascal, F.A.C.P., Havana, Cuba, is now President of the Cuban Society of Public Health. Not long ago, Dr. Abascal was awarded the honorary degree of Doctor of Science by Jefferson Medical College of Philadelphia.

The Commission on Professional and Hospital Activities, a new Commission organized and directed by representatives from the American College of Physicians, the American College of Surgeons, the American Hospital Association, and the Southwestern Michigan Hospital Association, and participated in by the American Medical Association, is now formally operating from headquarters in Ann Arbor, Michigan, under the Directorship of Dr. Vergil N. Slee (Associate). The American College of Physicians' Commissioners include Dr. C. Wesley Eisele, F.A.C.P., Denver, Colo., and Dr. Eliot E. Foltz, F.A.C.P., Chicago, Ill. Dr. Paul Hawley of the American College of Surgeons has been elected President of the Commission. The Executive Committee consists of Dr. Hawley, Dr. Robert Meyer of the American College of Surgeons, Dr. Edwin Crosby of the American Hospital Association, and Dr. Eliot E. Foltz, F.A.C.P., of the American College of Physicians.

The purpose of the new Commission is to conduct hospital audits and to furnish prompt and efficient medical record analyses of hospitals. The W. H. Kellogg Foundation is providing certain necessary funds for the first three years after which it is anticipated the Commission will be self-supporting.

Dr. Francis M. Pottenger, Sr., M.A.C.P., Emeritus Professor of Medicine, University of Southern California School of Medicine, and Medical Director, The Pottenger Sanatorium and Clinic, Monrovia, was presented with a leather-bound volume of more than 435 letters sent to him from all over the world. This was presented to him as a surprise at a dinner meeting of the Los Angeles County Medical Association, where he addressed the physicians on "One Hundred Years in the Prevention and Treatment of Tuberculosis."

Dr. Pottenger has practiced for sixty years in the Los Angeles County area, and established the first private sanatorium in Southern California, known as The Pottenger Sanatorium and Clinic (1903), organized the Southern California Antituberculosis League (1902), and founded the Christmas Seal movement in Los Angeles County, in 1909.

Dr. Garfield G. Duncan, F.A.C.P., was presented with a ship's bell by the registrants in the American College of Physicians' Postgraduate Course, "Some Recent Developments in Principles and Practice of Modern Medicine," directed by Dr. Duncan for the College at the Pennsylvania Hospital, May 14–18, 1956. Engraved on the bell was the following: "Presented to Dr. and Mrs. Garfield G. Duncan, 'Donachaidh,' Postgraduate Course No. 5, American College of Physicians, Pennsylvania Hospital, May 14–18, 1956." "Donachaidh" is the name of Dr. Duncan's country home at which he entertained the members of the class one evening during the course. There were 121 physicians registered in the course.

Dr. Emilie V. Rundlett, F.A.C.P., of Denville, N. J., was awarded an honorary degree of Doctor of Laws from Seton Hall University at its one-hundredth Commencement, on June 9. Dr. Rundlett received the degree for her meritorious work as Director of the Communicable Disease Division of the Jersey City Medical Center for the past 34 years, and for her help in coördinating the new Seton Hall College of Medicine with the Jersey City Medical Center.

Dr. Harold J. Jeghers, F.A.C.P., has accepted the appointment as Professor of Medicine at the new Seton Hall University School of Medicine at Jersey City, N. J., effective August 1. Dr. Jeghers was previously Professor of Medicine and Director of the Department of Medicine at Georgetown University School of Medicine, Washington, D. C. In addition to his new appointment, he will serve as Consultant to the Department of Medicine at Georgetown University School of Medicine.

Dr. Clarence E. Hufford, F.A.C.P., Toledo, Ohio, was awarded the Distinguished Medal and Certificate of the American Cancer Society. In addition to his duties as Consultant, X-ray Department, St. Vincent's Hospital, Dr. Hufford is Chairman of the College Liaison Committee, American Heart Association, and President of the Radiological Society of North America.

Dr. John R. Snavely, (Associate), Jackson, Miss., Professor and Chairman of the Department of Medicine, University of Mississippi School of Medicine, has accepted the appointment as Assistant Dean of that institution. Before coming to the University of Mississippi School of Medicine, Dr. Snavely was Associate Professor of Medicine at Tulane University of Louisiana School of Medicine, New Orleans.

Dr. Russell S. Boles, Sr., F.A.C.P., Emeritus Professor of Clinical Medicine, University of Pennsylvania School of Medicine, has recently been appointed Honorary Consultant, Department of Medicine, Philadelphia General Hospital.

Dr. Hugh Montgomery, F.A.C.P., Philadelphia, has been elected President of the Heart Association of Southeastern Pennsylvania, succeeding Dr. Samuel Bellet, F.A.C.P., Philadelphia. Other newly-elected officers are: Dr. George D. Geckeler, President-Elect; Dr. John E. Deitrick, F.A.C.P., Vice President; Mr. Warner F. Haldeman, Secretary and Executive Director; Mr. Clement A. Griscom, III, Treasurer; Mr. Leon J. Obermayer, Solicitor.

Dr. Richard J. Bing, F.A.C.P., Birmingham, Ala., has been appointed Chief of the Washington University Medical Services Division at the Veterans Administration Hospital and Professor of Medicine, Washington University School of Medicine, St. Louis. Before his appointment to Washington University School of Medicine, Dr. Bing was Professor of Experimental Medicine and Clinical Physiology at the Medical College of Alabama.

Dr. Ramón M. Suárez, Sr., F.A.C.P., San Juan, P. R., recently received two honors: The Lions Club of San Juan presented him with the "Dr. J. Gonzalez Martinez Award," which consisted of a beautifully engraved diploma and a gift of laboratory apparatus for the Laboratorios de la Fundacion de Investigaciones Clinicas, of which Dr. Suárez is the Founder and Director; The International Lions Club presented him with a Bronze Plaque and Key, known as the "Eugenio Maria de Hostos" award for distinguished service, as Puerto Rico's first citizen in civic affairs for the year 1956.

Dr. Henry B. Mulholland, F.A.C.P., Assistant Dean and Professor of Internal Medicine, University of Virginia School of Medicine, Charlottesville, has been appointed Chairman of the reorganized Committee on Aging of the American Medical Association. The Committee will study the problems of medicine in relation to the increasing numbers of our aging population, with particular emphasis on appropriate vocations, homes and places of rest, and necessary recreational facilities.

Two Fellows of the College were elected to office in the New York State Medical Society at their recent Annual Meeting. Dr. Walter P. Anderton, F.A.C.P., New York, Secretary, and Dr. Maurice J. Dattelbaum, F.A.C.P., Brooklyn, Treasurer. Other newly-elected officers of the Association are: Dr. James Greenough, Oneonta, President; Dr. Thurman B. Givan, Brooklyn, President-Elect; Dr. Thomas M. Watkins, Potsdam, Vice President; Dr. Ezra A. Wolff, Forest Hills, Assistant Secretary, and Dr. Samuel Z. Freedman, New York, Assistant Treasurer.

Col. James H. Forsee, Sr., F.A.C.P., (MC), U. S. Army, has been assigned the dual responsibility as Assistant Chief of the Professional Division and as Chief Surgical Consultant, Office of the Surgeon General, U. S. Army, Washington, D. C.

Dr. Herman Beerman, F.A.C.P., was reëlected as Secretary Treasurer of the Society for Investigative Dermatology, at their Annual Meeting held at Chicago, June 9-10. Other officers of the Society are: Dr. Maximilian E. Obermayer, Los Angeles, President; and Dr. Rudolf L. Baer, New York, Vice President.

Dr. Walter B. Shelley, F.A.C.P., Philadelphia, and Dr. Francis J. Ellis, Baltimore, were appointed for a term of five years (1956-61), to serve on the Board of Directors of that Society.

Lt. Col. Marion E. McDowell, (Associate), (MC), U. S. Army, has been awarded a Certificate of Achievement for his "... outstanding record of service well

rendered" to his country. The award praised Col. McDowell for his contributions in Korea "to the understanding of the complex problems of shock and renal failure in hemorrhagic fever," as well as "steadfast devotion to duty at Walter Reed Army Medical Center."

Dr. Leandro M. Tocantins, F.A.C.P., Professor of Clinical and Experimental Medicine and Director of the Charlotte Drake Cardeza Foundation, Jefferson Medical College of Philadelphia, spoke on "Endocrinological Aspects of Disorders of the Blood" at the Seventh Annual Postgraduate Session of the Barbour-Randolph-Tucker Medical Society, held at Elkins, W. Va.

Dr. Samuel B. Hadden, F.A.C.P., Associate Professor of Psychiatry, University of Pennsylvania School of Medicine, has recently returned from a lecture tour in Mexico. While in Mexico, Dr. Hadden lectured before the Mexican Society of Neurology and Psychiatry on the topic of "The Dynamics of Group Psychotherapy," and also spoke before the Guadalajara Medical Society on the related fields of Neurology and Psychiatry.

Dr. Perk Lee Davis, F.A.C.P., Paoli, represented the Presbyterian Hospital of Philadelphia and the Paoli Medical Center at the Third National Cancer Conference, held at Detroit, Mich.

Dr. Michael M. Dacso, (Associate), New York, N. Y., Associate Professor of Clinical Physical Medicine and Rehabilitation, New York University College of Medicine, served as Consultant in Medicine and Rehabilitation at the Federal-State Conference on Aging, held at Washington, D. C., June 5-6.

Dr. Ellis H. Hudson, F.A.C.P., Cedar Grove, Wis., participated in the program of the First International Symposium on Venereal Diseases and the Treponematoses, held under the sponsorship of the World Health Organization, May 28-June 1, at Washington, D. C.

Rear Admiral Bartholomew W. Hogan, F.A.C.P., Surgeon General of the U. S. Navy, attended the inaugural ceremonies of the new Peruvian Medical Center, held July 4, at Lima, Peru.

The Fifth Meeting of the International Congress of Gastroenterology was held at London, England, July 18-21. The main subjects for discussion were Non-malignant Conditions of the Oesophagus and Ulcerative Colitis.

Several members of the College were in attendance: Dr. Mandred W. Comfort, F.A.C.P., Rochester, Minn.; Dr. Albert M. Snell, F.A.C.P., Palo Alto, Calif.; Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa.; and Dr. C. Wilmer Wirts, F.A.C.P., Philadelphia, Pa.

Dr. William D. Stroud, F.A.C.P., A.C.P. Treasurer, and Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, gave a paper entitled "The Diagnosis and Treatment of Coronary Artery Disease," at the Annual Meeting of the Kentucky Heart Association, held June 28, at Louisville, Ky.

Dr. Samuel Epstein, F.A.C.P., Brooklyn, presented a paper on June 10, entitled "Observations on Clubbed Fingers," before the American College of Angiology, held at Chicago. On June 13, he presented a paper entitled "Is the Post-Commissurotomy Syndrome of Rheumatic Origin?", at the Section on Internal Medicine of the American Medical Association.

Dr. Franklin K. Paddock, F.A.C.P., Pittsfield, Mass., has been named Chief of Staff at the Pittsfield General Hospital, a position formerly filled by both his father, the late Dr. Bruce W. Paddock, and his grandfather, Dr. William L. Paddock, who was the Hospital's first Chief of Staff, and served there when it was established in 1874, and then known as the House of Mercy.

The Second Congress of the World Confederation for Physical Therapy was held at New York City, June 17-24, with an attendance of 2,199, exclusive of exhibitors. Thirty-nine countries were represented, all but five by physical therapists. Turkey, Portugal, Korea, Russia and Argentina were represented by physicians. Proceedings of the Congress will be published around the first of the coming year and will be available at a cost of \$3.00, postpaid.

Dr. Nathaniel E. Reich, F.A.C.P., Clinical Assistant Professor of Medicine, State University of New York College of Medicine at New York City, served as moderator of a panel on "Heart Function" at the Fourth International Congress of the American College of Chest Physicians, held at Cologne, Germany, Aug. 22. The panel consisted of prominent Cardiologists from six countries.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

John Eugene Gonce, Jr., M.D., F.A.C.P., March 25, 1956, Madison, Wis. Clifford Brewster Brainard, M.D., F.A.C.P., May 7, 1956, West Hartford, Conn. George Stirling Landon, M.D., F.A.C.P., May 21, 1956, San Bernardino, Calif. James Warren Laws, M.D., F.A.C.P., June 15, 1956, El Paso, Texas Edward W. McCloskey, M.D., F.A.C.P., June 16, 1956, Philadelphia, Pa. Lawrence Greenman, M.D., (Associate), June 20, 1956, Pittsburgh, Pa. Harry Jay Epstein, M.D., F.A.C.P., July 9, 1956, Philadelphia, Pa.

DR. JAMES ALEXANDER LYON

Dr. James Alexander Lyon, F.A.C.P., Washington, D. C., was born in Broome County, New York, February 28, 1882. He attended Ohio University and transferred to Maryland Medical College, Baltimore, from which he received his medical degree in 1906; subsequently he did postgraduate work in London, Vienna and at Harvard University. He interned at Franklin Square and Bay View City Hospitals (Baltimore) 1906–07; Resident Physician, Loomis Sanatorium (Liberty, N. Y.), 1907–09; Senior Resident Physician and Assistant Superintendent, Rutland State Sanatorium, (Mass.), and Attending Physician, Outpatient Department, Massachusetts General Hospital (Boston), 1909–16.

Dr. Lyon was commissioned a First Lieutenant in the Medical Corps of the United States Army in 1916; served on the Mexican Border, 1916–17; served with A.E.F., 1917–19, as Commanding Officer of the U. S. Army Hospital, 1st Corps Area, France, and as a Senior Surgeon with the 26th Infantry Division. Following World War I, he held numerous appointments in the United States. Dr. Lyon was the recipient of numerous citations and decorations, including the Purple Heart and Silver Star. He resigned from the Army in 1925 with the rank of Major.

Dr. Lyon served as Professor of Clinical Cardiology, Georgetown University School of Medicine, 1929–40; Cardiologist and Chief of Cardiac Clinic, Central Dispensary and Emergency Hospital and Children's Hospital, 1929–40; Attending Physician, Outpatient Department, Johns Hopkins Hospital (Baltimore), 1924–25; Consulting Cardiologist and Member of Executive and Teaching Staff, Doctors Hospital; Cardiologist, Sibley Memorial Hospital.

Dr. Lyon was President of the American Therapeutic Society, 1950-51; twice President of the Pan American Society of the District of Columbia; Trustee, Pan American Medical Association; first Secretary and third President, Washington, D. C. Heart Association; former Treasurer and Member of the Board of Directors, International Medical Society; past National Surgeon General of the Military Order of Foreign Wars. He had been a Fellow of the American College of Physicians since 1930, and became a Life Member in 1939. He died on August 3, 1955, aged 73, of adenocarcinoma of the sigmoid colon.

E. R. LOVELAND, Executive Secretary

DR. DANIEL THOMPSON McCALL, SR.

Dr. Daniel Thompson McCall, Sr., F.A.C.P., of Mobile, Ala., died November 9, 1955. Dr. McCall was born in DeSotoville, Ala., in 1869. He received his A.B. degree from the University of Alabama in 1887, and his M.D. degree from Louisville Medical College in 1894. He took postgraduate studies in Pediatrics at the Postgraduate Medical School in New York, Postgraduate Medical School of Chicago, Polyclinic Medical School, Philadelphia, and Harvard Medical School, Boston. From 1894 on, Dr. McCall had a private practice in general medicine, and not until after his postgraduate studies in 1909 did he specialize in the field of Pediatrics. Dr. McCall then became Professor of Pediatrics at the Medical College of Alabama from 1914–18, and later Dean until 1920 when the College was moved to Tuscaloosa, Ala. During World War I, he was a volunteer with the Medical Service Corps, and after this for many years Dr. McCall was a member of the Staff at the Providence Hospital and Mobile Infirmary.

He was a member of the Mobile County Medical Society, Medical Association of the State of Alabama, Southern Medical Association, the American Medical Association, President of the American Pediatric Society, (1925–26), and a Fellow (1927) of the American College of Physicians.

Dr. McCall was Choctaw County Health Officer from 1898–1907, and Secretary-Treasurer of the Choctaw County Medical Society from 1898–1907. He was a former President of the Mobile County Board of Health and a member of the Alabama State Board of Health from 1926–31, also a member of the Alabama State Board of Censors and Medical Examiners from 1923–33. Dr. McCall served as State Senator from 1939–43, and as a member of the Alabama State Board of Education from 1918–35.

He is survived by his wife, Mrs. Caroline B. McCall, of 1901 Government St., Mobile, and two sons.

D. O. WRIGHT, M.D., F.A.C.P., Governor for Alabama, A.C.P.

DR. WILLIAM EGBERT ROBERTSON

After a long illness, Dr. William Egbert Robertson, F.A.C.P., died on March 9, 1956. Dr. Robertson was born in Camden, New Jersey, July 1, 1869. He graduated from the University of Pennsylvania in 1892. In his day, pathology was a great training ground for clinicians and in line with this viewpoint, Dr. Robertson prepared himself for his distinguished career by doing postgraduate work in pathology at Heidelberg and Vienna Universities.

He began his academic career as Physician to the Outpatient Department of the University of Pennsylvania. Soon, however, he became Pathologist and Visiting Physician to the Episcopal Hospital, Visiting Physician to Temple University Hospital and to the Germantown Dispensary and Hospital. In time, he became Medical Chief of St. Luke's and Children's Medical Center and was a Chief of Service at the Philadelphia General Hospital and Physician to the Northeastern Hospital. Among the academic titles which he held were Associate Clinical Professor of Medicine, Medico-Chirurgical College and Hospital; Professor of Medicine, Temple University School of Medicine; Emeritus Professor of Medicine, Temple University.

Dr. Robertson was a member of the College of Physicians of Philadelphia, his

County and State Medical Societies and of the American Medical Association. He was President of the Philadelphia County Medical Society in 1937. Other societies of which he was also a member were the Medical Literature Club, the Philadelphia Clinical Association and the Northern Medical Society. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1920. Those of us who knew Dr. Robertson well will perhaps remember him best for his wide knowledge not only of medicine but of literature, also. He was an omnivorous reader with very broad interests who could talk interestingly and intelligently on almost any subject. Even after he was stricken with hemiplegia and was forced to give up practice, he never lost his broad interest. At the time he was forced to retire in 1949, it is true that he was "an old physician" in years. We who knew him well, however, never thought of him as an "old physician"; for he was not one who clung to old teaching and old ways but one who knew and accepted the newest and latest advances.

Most of Dr. Robertson's contemporaries have passed on but many of us of a somewhat younger generation remember him with affection and respect. Dr. Robertson is survived by his son, Dr. Harold F. Robertson of Philadelphia and sister, Mrs. William C. Lynch.

THOMAS M. McMillan, M.D., F.A.C.P., Governor for Eastern Pennsylvania, A.C.P.

DR. WILLIAM WARNER WATKINS

Dr. W. Warner Watkins, F.A.C.P., died April 10, 1956 at his home in Phoenix, Arizona, from carcinoma of the sigmoid with metastases to the liver, at the age of 72 years. He had remained active in his specialty of Radiology up to a few months before his death.

Born in Keysville, Va., October 30, 1883, he graduated from the Medical College of Virginia in 1906, coming to Metcalf, Arizona as a general practitioner. In 1907 he moved to Phoenix, and in 1914 organized the Pathological Laboratory, which for many years provided the most modern and complete laboratory and x-ray facilities in the Southwest. He acted as Radiologist for St. Joseph's Hospital 1914–41, and St. Luke's Home since 1941. He was Radiologist at Good Samaritan Hospital 1925–1941, and Consulting Radiologist to the Arizona Industrial Commission, 1934–49. He later became associated with the Medical Center X-ray and Clinical Laboratory as well as the Professional Laboratory.

He was a member of the Maricopa County, Arizona State, Southwestern, and American Medical Associations as well as the American and Pacific Coast Roentgen Ray Societies, the American Medical Editors' Association, Radiological Society of North America, American College of Radiology, American Association for the Advancement of Science, Diplomate, American Board of Radiology, Fellow (1921), Life Member (1944) and Governor for Arizona, American College of Physicians.

He held numerous offices including Secretary and President of the Maricopa County and Arizona State Medical Associations, Vice-President and President of the Southwestern Medical Association, Vice-President and Corresponding Secretary, Pacific Coast Roentgen Ray Society, Vice-President, Radiological Society of North America, Chancellor, American College of Radiology, and President of the Phoenix Clinical Club.

He was Editor of Southwestern Medicine and author of numerous articles published in various medical journals. He was the author of "A Christian Philosophy of Life" published by the Judson Press, Philadelphia.

An active church worker, Dr. Watkins was a member of the First Baptist Church in Phoenix, and had held both State and National offices in the American Baptist Convention. He was interested in young people and worked on many projects for them. He was a member of the Social Service Board of the Cook Christian Training School and active in the Y.M.C.A.

In 1951, Dr. Watkins was honored by the Arizona State Medical Association, for 50 years of outstanding service, especially for his work with the Arizona State Tuberculosis Association. His passing removes one of the real pioneers of modern medicine from the active rolls of Arizona medicine. A physician who will be long remembered for his honesty, kindliness, and professional ability.

He is survived by his wife Mrs. Bess Thomas Watkins of 206 East Moreland Street, Phoenix, Arizona.

LESLIE R. KOBER, M.D., F.A.C.P., Governor for Arizona, A.C.P.

DR. LESLIE RICHARD WEBB, SR.

Dr. Leslie Richard Webb, Sr., F.A.C.P., died in Springfield, Mo., on February 29, 1956, at the age of 72. He was born in Mt. Moriah in 1883. Dr. Webb received his M.D. degree from Drake University College of Medicine in 1909 and served his internship at the Mercy Hospital in Des Moines, Iowa.

He took postgraduate studies at Chicago Postgraduate College, Illinois Postgraduate Medical College, Jefferson Medical College, University of Pennsylvania Postgraduate Medical School, Washington University and Harvard Medical School, from which he derived great pleasure, particularly in gastro-enterology and in psychiatry.

Dr. Webb was an Associate on the staffs of St. John's and Springfield Baptist Hospitals from 1920, and Chief of the Medical Staff of Burge Hospital from 1925 until his death. He was a Diplomate of the American Board of Internal Medicine and a Fellow (1925) and Life Member (1947) of the American College of Physicians.

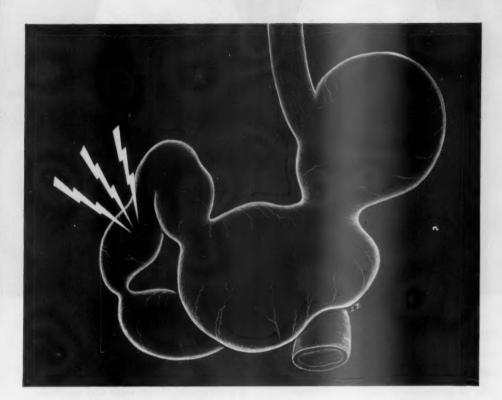
Dr. Webb was also a member of the Greene County Medical Society, Missouri State Medical Society, the American Medical Association, Southern Medical Society, Radiological Society of North America, the National Gastroenterological Association, and the American Geriatric Society.

He was a conscientious, hard-working doctor who took splendid care of his patients and also managed to devote a great deal of time to keeping abreast of new developments in medicine.

Dr. Webb is survived by his wife, Mrs. Clare D. Webb of 1254 East Meadowere St., Springfield, and his son Dr. L. Richard Webb, an internist who had practiced with him for a number of years.

CARL V. MOORE, M.D., F.A.C.P., Governor for Missouri, A.C.P.

PRO-BANTHINE FOR ANTICHOLINERGIC ACTION



Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations^{1,2} on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

"... abnormal motility² is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

Pro-Banthine⁸ has been demonstrated consistently to reduce hypermotility of the stomach and intestinal tract and in most instances also to reduce gastric acidity. Dramatic remissions in peptic ulcer have followed Pro-Banthine therapy. These remissions (or possible cures) were established not only on the basis of the disappearance of pain and increased subjective well-being but also on roentgenologic evidence.

Pro-Banthine Bromide (Beta-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) has other fields of usefulness, particularly in those in which vagotonia or parasympathotonia is present. These conditions include hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm.

Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology 25:416 (Nov.) 1953.

Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology 23:252 (Feb.) 1953.





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 Martin, W. J., et al.: J.A.M.A. 160:925 (March 17) 1956. PEN·VEE·Oral and PEN·VEE Suspension permit new dependability in oral-penicillin therapy—dependable stability in gastric acid, dependable and optimal absorption in the duodenum. "Not being destroyed by acid in the stomach, as is penicillin G, penicillin V remains available in larger amounts for absorption."

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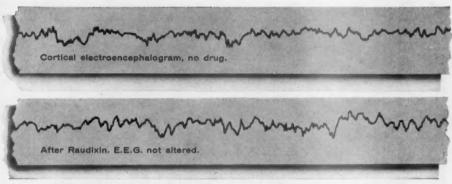
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supply: 50 mg. and 100 mg. tablets, bottles of 100, 1000 and 5000.

"RAUDIXIN" IS A SQUIBB TRADEHARK

THE AMERICAN COLLEGE OF PHYSICIANS Schedule of Postgraduate Courses, Autumn, 1956

	0	October	er		Nove	November	<u> </u>		December	mpe	E.		Fe	February 1957	
The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, \$30.00; Non-members, \$60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.	21-8	61-51	22-26 \$\dagger{4}\$ \dagger{4}\$	6-5	12-16	19-23	08-97	8–8	₱1-01	17-21	24-29	31-Jan. 4	8-4	18-22	
Course No. 1, RECENT ADVANCES IN CARDIOVASCULAR DISBASES: Mt. Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-directors.	×											1	1		
Course No. 2, SEMINARS IN INTERNAL MEDICINE: Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., M.A.C.P., Co-directors.	×										1	1		1	
Course No. 3, CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director.		×	1								1	1			
Course No. 4, RECENT ADVANCES IN INTERNAL MEDICINE: University of Washington School of Medicine, Scattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.			×	1		ng Week		1			S Week		1: 11	1	
Course No. 5, SELECTED PROBLEMS IN INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., Director.		1	1	1	1	anksgivi	×				semteind.			1	
Course No. 6, GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.				1	1	4.L		3-7	1	1)	1		1	1
Course No. 7, ELECTROCARDIOGRAPHY: University of Utah College of Medicine and Salt Lake County General Hospital, Salt Lake City, Utah; Hans H. Hecht, M.D., Director.	İ	1	1	1		1		×	1	I	1				1
Course No. 8, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS: Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., (Associate), and Edward H. Reinhard, M.D., (Associate), Co-directors.				1	1						-	1		1	×



= sound ulcer therapy

provides prolonged relief of ulcer pain.1

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This combination of ulcer-combating ingredients in pleasanttasting KOLANTYL Gel, or convenient tablets, makes rational its use as the medication of choice in peptic ulcer therapy.



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Rapid, Prolonged Antacid Relief
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Hydroxide Gel400 mg.

Magnesium Oxide200 mg.

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Dosage:

Gel — 2 to 4 teaspoonfuls every three hours, or as needed. Tablets — 2 tablets (chewed for more rapid action) every three hours, or as needed.

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 Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953.
 McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

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References: I. Bhrlich, J. C.: Arizona Med. 12: 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. 227: 188 (Peb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. 39: 1199 (Dec.) 1953. 4. Hejtmanelk, M. R., and Herrmann, G. R.: Texas St. J. M. 51: 238 (May) 1955. 5. Battermann, R. C.; DeOraff, A. C., and Rose, O. A.: Circulation 5: 201 (Feb.) 1952. 6. Denham, R. M.: J. Kontucky St. M. Amec. 53: 209 (Mar.) 1955.

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Bender, M. J., et al.: Am. Jour. Med., 18:622, Apr., 1955. Z. Samson, J. J., and Zipest, Alberti Girculattion, 9:38, Jan., 1954. 3. Nichol, E. S., in Com., H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. 4. Jamieson, W. L., et al., Jour. Am. Gerlat, Sco., 1954, h. Mer., 1955. 5. Gilchuist, A. Rae: Brit. Med. Jour., 2059, Aug., 1955. 5. Gilchrist, A. Rae: Brit. Med. Jour., 2059, Aug., 1955.

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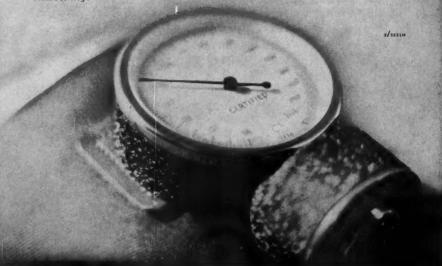
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¹January, H. L. et al: Clinical experience with tetracycline. Antibiotics Annual 1954-56, p. 625.



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1. New and Nonofficial Remedies. J.B. Lippincott Co., Philadelphia, 1956, p. 328. 2. Osol, A., and Farrar, G.E., Jr.: The Dispensatory of the United States of America. J.B. Lippincott Co., Philadelphia, 1956, pp. 808-809.





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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).

2.Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).

3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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LITERATURE AND SAMPLES ON REQUEST.

 Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, A Superior Hypotensive-Tranquilizer. In press.

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*Levist, T.: The Thyroid, London, E. and S. Livingstone, Ltd., 1954, p. 360.

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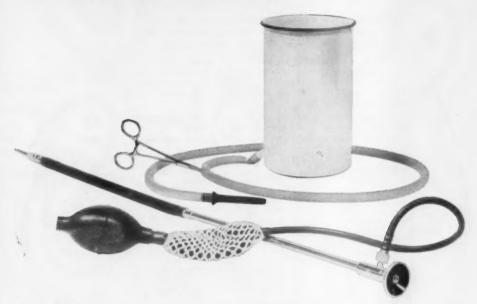
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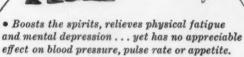
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